

The effectiveness of infrainguinal percutaneous transluminal angioplasty in the treatment of critical limb ischaemia

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Academic Dissertation

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List of original publications

- I** KORHONEN M, BIANCARI F, SÖDERSTRÖM M, ARVELA E, HALMESMÄKI K, ALBÄCK A, LEPÄNTALO M, VENERMO M. *Femoropopliteal balloon angioplasty vs. bypass surgery for CLI: a propensity score analysis*. European Journal of Vascular and Endovascular Surgery 2011; 41: 378–84.
- II** SÖDERSTRÖM M, ARVELA EM, KORHONEN M, HALMESMÄKI KH, ALBÄCK AN, BIANCARI F, LEPÄNTALO MJ, VENERMO MA. *Infra-popliteal percutaneous transluminal angioplasty versus bypass surgery as first-line strategies in critical leg ischemia: a propensity score analysis*. Annals of Surgery 2010; 252: 765–73. (Published previously in the academic dissertation, ‘Critical leg ischaemia with tissue loss - a challenge for the vascular surgeon’, by Maria Söderström)
- III** KORHONEN M, HALMESMÄKI K, LEPÄNTALO M, VENERMO M. *Predictors of failure of endovascular revascularization for CLI*. Accepted for publication in the Scandinavian Journal of Surgery.
- IV** KUKKONEN T, KORHONEN M, HALMESMÄKI K, LEHTI L, TIITOLA M, AHO P, LEPÄNTALO M, VENERMO M. (2010) *Poor inter-observer agreement on the TASC II classification of femoropopliteal lesions*. European Journal of Vascular and Endovascular Surgery 2010; 39: 220–4.
- V** KORHONEN M, LEPÄNTALO M, VENERMO M. *Quality of referrals and decision making during angiography for patients with critical limb ischemia*. (Submitted, Scandinavian Journal of Surgery)

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Abbreviations

ABI	Ankle-brachial index
AFS	Amputation-free survival
AP	Ankle pressure
BASIL	Bypass versus angioplasty in severe ischaemia of the leg
CAD	Coronary artery disease
CI	Confidence interval
CLI	Chronic critical limb ischaemia
CTA	Computed tomography angiography
CVD	Cerebrovascular disease
DD	Colour-assisted duplex ultrasonography
DSA	Digital subtraction angiography
eGFR	Chronic kidney disease class according to estimated glomerular filtration rate
HDL	High-density lipoprotein
HR	Hazard ratio
IC	Intermittent claudication
ISCVS	International Society for Cardiovascular Surgery
LDL	Low-density lipoprotein
MI	Myocardial infarction
MRA	Magnetic resonance angiography
PIII	PRoject of Ex-Vivo vein graft ENgineering via Transfection III (PREVENT III)
PAD	Peripheral arterial disease
PTA	Percutaneous transluminal angioplasty
RCT	Randomized controlled trial
ROC	Receiver operating characteristic
RR	Risk ratio
SFA	Superficial femoral artery
SLI	Severe leg ischaemia
SVS	Society for Vascular Surgery, USA
TASC	Trans Atlantic Inter-Society Consensus
tcPO₂	Transcutaneous partial pressure of oxygen
TP	Toe pressure

CRITICAL LOWER LIMB ISCHAEMIA (CLI) is the most severe form of peripheral arterial disease (PAD). Even though the treatment of CLI has evolved during the last decade, CLI is still associated with considerable morbidity, mortality and decreased quality of life, in addition to a large financial impact on society. Infrainguinal bypass surgery has traditionally been considered the approach of choice for treating CLI patients in order to avoid amputation. However, there are increasing data on the efficacy of endovascular revascularization procedures to achieve good leg salvage rates as well.

The main aim of the present study was to compare percutaneous transluminal angioplasty (PTA) and bypass surgery in the treatment of CLI. Additionally, predictors of the failure of PTA for CLI were sought, the reproducibility of the TASC II classification of femoropopliteal arterial lesions was tested and communication between vascular surgeons and interventional radiologists was evaluated.

Data gathered on all the 2,054 CLI patients revascularized at the Helsinki University Central Hospital between 2000 and 2007 were analyzed retrospectively. This patient cohort was used to compare the results of PTA and bypass surgery as well as to investigate predictors of failure after PTA. Propensity scores can be used for identifying patients with similar chances of receiving one treatment or the other, thus permitting non-randomized comparisons of treatment outcomes. Consequently, the propensity score analysis was used for regression adjustment and for one-to-one matching in the studies comparing PTA and surgical revascularization. To test the TASC II classi-

Abstract

fication, 200 angiographies were evaluated by seven investigators, comprising vascular surgeons and radiologists. Finally, 351 consequent referrals made by vascular surgeons to radiologists for digital subtraction angiography (DSA) with or without a request for an intervention at the Helsinki University Central Hospital during 2007 were scrutinized. These and the procedures performed accordingly at the Department of Radiology were evaluated.

When the treatment method was adjusted for propensity score as well as in the propensity-score-matched pairs, infrainguinal PTA and bypass surgery yielded similar results at 5 years in terms of survival, amputation-free survival (AFS) and freedom from any re-interventions. However, when the femoropopliteal segment was treated, leg salvage was significantly better in the surgical revascularization group at 5 years, whereas no significant difference was observed between the two treatment methods when the revascularization extended to the infrapopliteal segment. Infrainguinally, PTA resulted in significantly lower freedom from surgical re-interventions when compared to surgical revascularization.

The patient's nonambulatory status upon hospital arrival was a significant predictor of death, amputation and surgical re-intervention after PTA. Gangrene was a significant predictor of amputation and was more strongly associated with it than the presence of an ulcer.

The inter-observer agreement on the TASC II classification of femoropopliteal lesions proved to be inadequate.

The informational content of the referrals made by vascular surgeons frequently proved to be inadequate. The radiologists

made treatment alterations at their own discretion in 20% of the instances, and these resulted in significantly more complications and/or technical failures than when the referral request was followed or a vascular surgeon was consulted beforehand.

In conclusion, when technically feasible, infrainguinal PTA seems to be a valid alternative for bypass surgery in the treatment of CLI when redo-surgery is actively utilized. However, at the femoropopliteal level, PTA might be associated with poorer leg salvage in the long term when compared to bypass surgery, although the treatment method did not affect AFS. Bypass surgery could likely be considered as a better alternative in patients with probable longevity.

Strong predictors of poor outcome after PTA for CLI are nonambulatory status upon hospital arrival and gangrene as a manifestation of CLI.

The TASC II classification of femoropopliteal arterial lesions allows individual interpretations, and its reproducibility seems to be rather poor. Its common use as a basis for therapeutic decision-making and reporting outcomes in scientific literature can therefore be questioned.

The communication between vascular surgeons and interventional radiologists seems to be insufficient to ensure optimal treatment for CLI patients. A mixed team approach could help decrease these problems. 🐼

Introduction and review of the literature

Chronic critical limb ischaemia

Introduction

Critical limb ischaemia (CLI) is the most severe form of peripheral arterial disease (PAD). In CLI there is lack of sufficient arterial blood flow to accommodate the metabolic requirements of the resting tissues, thus threatening the viability of the distal extremities. This is usually caused by multilevel arterial occlusive disease, frequently involving the infrainguinal vessels (VEITH ET AL. 1990). As the population is aging and the amount of diabetic patients growing, CLI presents an expanding challenge for the health care system (HIRSCH ET AL. 2008, SHAW ET AL. 2010). Even though advances in the treatment of CLI have been made during the last decade, the prognosis of CLI patients remains poor. CLI is associated with considerable morbidity, mortality and a decreased quality of life, in addition to a large financial impact on society (NORGREN ET AL. 2007).

Definition of CLI

CLI is defined as ischaemic rest pain persisting at a level requiring analgesics for at least 2 weeks or non-healing pedal ulcers or gangrene attributable to objectively proved arterial occlusive disease (DORMANDY ET AL. 2000, NORGREN ET AL. 2007, SECOND EUROPEAN CONSENSUS DOCUMENT 1991). In the North American recommendations for reporting standards (RUTHERFORD ET AL. 1997), CLI is equivalent to the grades II and III which include the categories 4, 5 and 6 (Table 1). Accordingly, in the classification of chronic limb ischaemia according to Fontaine (FONTAINE ET AL. 1955), stages III and IV represent CLI (Table 2).

There are varying recommendations regarding the level of objective circulatory impairment that is required to qualify for CLI (SECOND EUROPEAN CONSENSUS DOCUMENT 1991, RUTHERFORD ET AL. 1997). De-

TABLE 1.
Clinical categories of chronic limb ischaemia according to Rutherford
 (MODIFIED FROM RUTHERFORD ET AL. 1997)

Grade	Category	Clinical description	Objective criteria
0	0	Asymptomatic — no haemodynamically significant occlusive disease	Normal treadmill or reactive hyperaemia test
	1	Mild claudication	Completes treadmill exercise; AP after exercise >50 mm Hg but at least 20 mm Hg lower than resting value
I	2	Moderate claudication	Between categories 1 and 3
	3	Severe claudication	Cannot complete standard treadmill exercise and AP after exercise <50 mm Hg
II	4	Ischaemic rest pain	Resting AP <40 mm Hg, flat or barely pulsatile ankle or metatarsal PVR; TP <30 mm Hg
III	5	Minor tissue loss — nonhealing ulcer, focal gangrene with diffuse pedal ischaemia	Resting AP <60 mm Hg, ankle or metatarsal PVR flat or barely pulsatile; TP <40 mm Hg
	6	Major tissue loss — extending above TM level, functional foot no longer salvageable	Same as category 5

AP, ankle pressure; PVR, pulse volume recording; TP, toe pressure; TM, transmetatarsal

pending on symptoms (rest pain or tissue loss), the Trans Atlantic Inter-Society Consensus (TASC) II suggests the use of absolute pressures of either ankle pressure (AP) less than 50–70 mmHg, toe pressure (TP) less than 30–50 mmHg or transcutaneous partial pressure of oxygen (tcPO₂) at the foot of less than 30–50 mmHg as the definition criterion for CLI (NORGREN ET AL. 2007).

Incidence and natural history of CLI

The incidence of CLI is not known with certainty. However, indirect evidence has been gathered from studies examining the progression of intermittent claudication (IC),

population surveys on prevalence as well as assumptions based on major amputations, and the thereby estimated incidence of CLI among the European population is 400–652 per 1 million every year (CATALANO 1993, CRITICAL LIMB ISCHAEMIA: MANAGEMENT AND OUTCOME 1995). As the population is ageing and the number of diabetics growing, the incidence of CLI is estimated to increase significantly in the future (ALLIE ET AL. 2009, SHAW ET AL. 2010).

The antecedent natural history of CLI is not well understood. It is appealing to assume that patients progress through the Fontaine stages in a stepwise manner – however, evidence from several studies suggests otherwise. For instance, a multi-center prospective study evaluating 713 pa-

TABLE 2.

Clinical classification of chronic limb ischaemia according to Fontaine
(MODIFIED FROM NORGREN ET AL. 2007)

Stage	Clinical description
I	Asymptomatic
IIA	Mild claudication
IIB	Moderate to severe claudication
III	Rest pain
IV	Ulceration or gangrene

tients requiring amputation for ischaemic disease showed that more than half the patients did not have any symptoms of leg ischaemia whatsoever in the preceding 6 months (DORMANDY ET AL. 1994). Although this study was not limited to CLI patients only, other studies have shown similar results (MÄTZKE AND LEPÄNTALO 2001, NEHLER ET AL. 2003). One possible explanation for this could be the co-morbidities of the CLI patients making them less likely to ambulate to an extent that would promote symptoms of claudication. In any case, these studies imply that the progression of PAD to CLI is unpredictable.

As the majority of patients presenting with CLI today receive some form of active treatment, it is no longer possible to describe the natural history of the disease. Those CLI patients who are unsuitable for reconstructive arterial surgery are not representative of the whole CLI patient population (LEPÄNTALO AND MÄTZKE 1996), and using their outcome as an indicator of the natural history of CLI is therefore skewed.

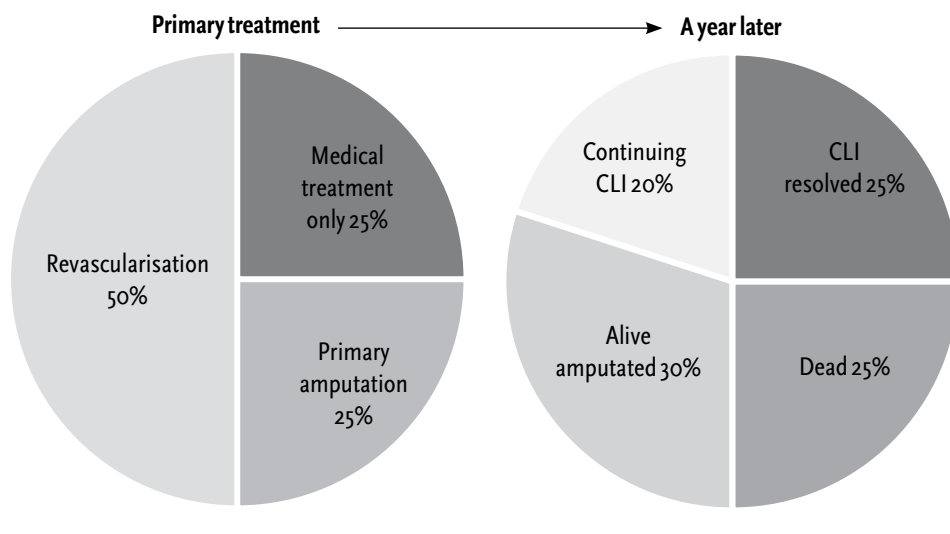
Fate of the patient with CLI

The severity of the systematic atherosclerosis

is accurately reflected by the severity of PAD. The prognosis for patients with CLI is indeed poor due to the diffuse multilevel nature of the arterial obstruction and concurrent cardiac and cerebrovascular co-morbidities (HIRSCH ET AL. 2006). Patients with severe PAD may have an up to 15-fold greater overall risk of cardiovascular mortality than those without the disease (CRIQUI ET AL. 1992). Approximately 80% of CLI patients will die from a vascular event, with the leading cause of death being myocardial infarction (MI) (JÄMSÉN ET AL. 2002, REGENSTEINER ET AL. 2002, WALKER ET AL. 1998). In a Finnish prospective study, the survival rate of 100 CLI patients treated with percutaneous transluminal angioplasty (PTA) was compared with that of the sex- and age-matched control population living in the same area, revealing a remarkable difference in favour of the control group (JÄMSÉN ET AL. 2002). The fate of the patient and the limb seems to depend on the severity of CLI. Within 10 years, the mortality of patients presenting with ischaemic rest pain can reach 80%–85% and of those with gangrene 95% (DORMANDY ET AL. 1999B, WALKER ET AL. 1998). In a review by Wolfe and Wyatt, 20 recent publications reporting the results of 6,118 patients with CLI were evaluated; the risk for limb loss at 1 year was estimated to be 70% for patients with rest pain and 95% for patients with tissue loss, if they were treated conservatively (WOLFE AND WYATT 1997).

Revascularization can significantly reduce the need for amputation for CLI patients (ESKELINEN ET AL. 2005, KUDO ET AL. 2006, LUTHER ET AL. 2000, WOLFE AND WYATT 1997). There are worldwide estimations that the primary amputation rate for CLI patients is 25%, and approximately 50% of patients with CLI will undergo some type of revascularization (NORGREN ET AL. 2007). Furthermore, one year thereafter roughly 25% of the patients will have died, some 30% will be alive with their leg amputated and approximately 20% will have continuing CLI (Figure 1).

FIGURE 1
Fate of the patients presenting with CLI
(MODIFIED FROM NORNGREN ET AL 2007).



Risk factors for CLI

Risk factors for developing CLI are similar to those of PAD (Table 3). Of these, the factors most strongly associated with the progression of PAD to CLI seem to be diabetes mellitus, cigarette smoking and age. These risk factors seem to be independent, and therefore the risk for developing CLI appears to be the sum of their effect (NORNGREN ET AL. 2007; Figure 2).

The ankle-brachial index (ABI) is an indicator of generalized atherosclerosis, for lower levels have been associated with higher rates of concomitant coronary artery disease (CAD) and cerebrovascular disease (CVD) as well as with the presence of cardiovascular risk factors (NEWMAN ET AL. 1993). ABI decreases as the functional severity of PAD increases, and the lowest ABI values are measured in legs with gangrene (ZIERLER ET AL. 2005). Consequently, decreasing ABI is associated with the risk of developing CLI (NORNGREN ET AL. 2007).

Diabetes

Diabetes is a strong risk factor for PAD, and diabetic patients are four times more likely to develop CLI than non-diabetic patients (NORNGREN ET AL. 2007). Almost half of the patients with CLI have diabetes; in a retrospective survey based on the Finnish national vascular registry (Finnvasc) including 5,709 operations for CLI, 44% of the patients were diabetics (VIRKKUNEN ET AL. 2004), with other studies revealing similar numbers (DICK ET AL. 2007). Yet, the number of diabetic patients is increasing dramatically, and it is estimated that diabetes affects 6.4% of the world's population and that the amount of diabetics will increase to 7.7%, thus affecting as many as 439 million adults by the year 2030 (SHAW ET AL. 2010).

The peripheral neuropathy associated with diabetes can mask ischaemic rest pain, leading to delayed diagnosis of CLI; diabetics have tissue loss as an indication for treatment for CLI more often than non-diabetics (VIRKKUNEN ET AL. 2004). Approximate-

ly 50% of diabetic foot ulcers are of neuroischaemic/ischaemic aetiology (GERSHATER ET AL. 2008, PROMPERS ET AL. 2007). The risk of developing gangrene is 20 to 30 times higher in diabetics with PAD when compared with non-diabetics with PAD (DORMANDY ET AL. 1999A). Diabetics are 5 to 10 times more likely to require an amputation than are non-diabetic patients (DORMANDY ET AL. 1999A, JUDE ET AL. 2001).

Diabetes predisposes to an infrageniculate atherosclerotic disease which may spread at an accelerated rate and lead to faster progression of intimal hyperplasia at anastomoses or angioplasty sites (DICK ET AL. 2007, DIEHM ET AL. 2006). The consequences of this are earlier and higher rates of re-stenosis after invasive treatment (DICK ET AL. 2007).

Smoking

Cigarette smoking is a powerful aetiological risk factor for PAD and is also strongly associated with the risk of developing CLI (CRIQUI ET AL. 1997, NORNGREN ET AL. 2007). The amount and duration of cigarette smoking correlate directly with the development and progression of PAD – heavy smokers have a four-fold higher risk of developing IC compared with non-smokers, and the diagnosis of PAD is made approximately a decade earlier in smokers than in non-smokers (DORMANDY ET AL. 1999, FREUND ET AL. 1993, NORNGREN

ET AL. 2007). A positive association between passive smoking and the prevalence PAD has additionally been demonstrated in a population-based cross-sectional survey of 1,209 Chinese female never-smokers (HE ET AL. 2008).

Dyslipidaemia

The lipid risk profile is similar between patients with PAD and those with CLI (DORMANDY ET AL. 2000). Elevated total and low-density lipoprotein (LDL) cholesterol and lowered high-density lipoprotein (HDL) cholesterol levels, as well as hypertriglyceridaemia are associated with PAD (FOWKES ET AL. 1992, MURABITO ET AL. 2002, NEWMAN ET AL. 1993). Yet, the evidence of dyslipidaemia as an independent risk factor for CLI is scarce and mostly extrapolated from studies on CAD.

Age

The incidence and prevalence of PAD increase sharply with advancing age (BAINTON ET AL. 1994, MEIJER ET AL. 1998), and age is also associated with the progression of PAD to CLI (DORMANDY ET AL. 1999A).

Diagnosis of CLI

Clinical presentation and physical examination

One of the cardinal symptoms in CLI is limb pain at rest, which presents as a burning dysesthesia of the foot and is typical-

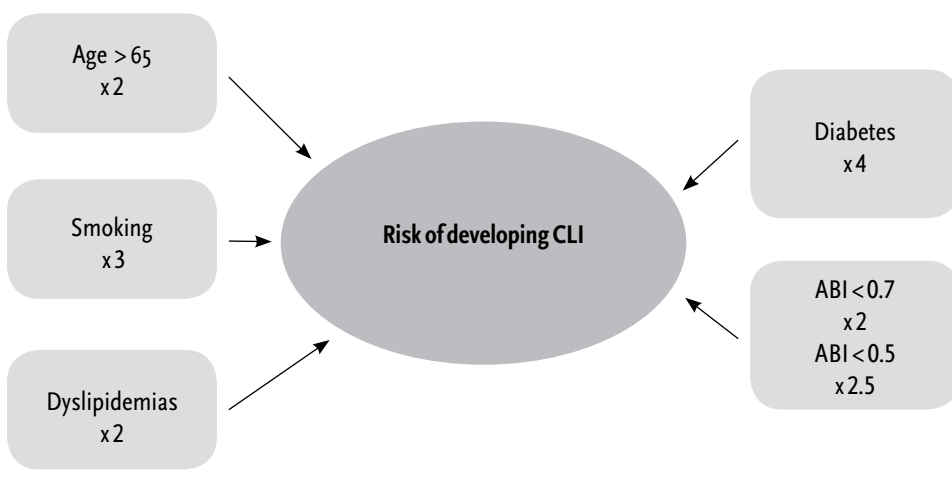
TABLE 3

Risk factors for peripheral arterial disease (MODIFIED FROM NORNGREN ET AL. 2007)

Cigarette smoking	Hyperhomocysteinaemia
Diabetes mellitus	Chronic renal insufficiency
Hypertension	Hyperviscosity and hypercoagulable states
Dyslipidaemia	Race (Asian/hispanic/black vs. white)
Elevated C-Reactive Protein	Sex

FIGURE 2

The approximate magnitude of the effect of risk factors on the development of CLI in patients with PAD
(MODIFIED FROM NORGREN ET AL. 2007)



ly aggravated by elevation and relieved with dependency (NEHLER AND WOLFORD 2005). It may be accompanied by pain caused by peripheral ischaemic neuropathy. Typically, narcotic analgetics are required to treat the pain. In diabetics this symptom of CLI may be masked by concomitant neuropathy, which impairs sensory feedback (NORGREN ET AL. 2007).

CLI may also present as an ischaemic skin lesion, that is, ulcer or gangrene. Some ulcers may be purely ischaemic in nature, whereas others may have other initial aetiologies such as trauma, venous insufficiency or neuropathy, but they fail to heal due to underlying PAD. An ischaemic ulcer is typically located in the tip of a toe or between toes, but may occur anywhere below mid-calf (BURKITT ET AL. 1998, HIRSCH ET AL. 2006). Additionally, an ischaemic ulcer characteristically has irregular margins and is dry, pale or pink-based and is painful in the absence of sensory neuropathy (HIRSCH ET AL. 2006, NORGREN ET AL. 2007). Gangrene typically affects the toes, but pres-

sure points, such as the heel, may also be affected. When severe, gangrene may involve the distal parts of the forefoot (NORGREN ET AL. 2007).

It is important to determine the time course of development of ischaemic symptoms, for CLI is rather a disease process that occurs in the chronic setting of months to years and is not to be confused with acute occlusion of the distal arterial tree. The vascular history should also include the assessment of arterial disease in other territories (especially CAD and CVD) and global risk factors for atherosclerosis (HIRSCH ET AL. 2006). By pulse palpation it may be possible to roughly estimate the level of significant arterial obstruction. If the pulse of both the dorsalis pedis and tibial posterior arteries is palpable, the possibility of a significant arterial disease is unlikely (LEPÄNTALO ET AL. 2000). Yet, the interpretation of pulse palpation may be more uncertain than generally believed (LUNDIN ET AL. 1999). The diagnosis of CLI should be confirmed with objective noninvasive testing; primarily by ABI and, when necessary, also by TP or tcPO₂ measurement (NORGREN ET AL. 2007).

Pressure measurements

Ankle pressure and the ankle-brachial index

The functional severity of PAD can be evaluated by measuring the ankle systolic blood pressure, which has become a standard part of the initial evaluation of patients with suspected PAD (NORGREN ET AL. 2007, ZIERLER ET AL. 2005). It is measured by placing a pneumatic cuff around the ankle just above the malleolus level, and the systolic blood pressure from both the dorsalis pedis and posterior tibial arteries is then recorded with a Doppler probe. However, the ankle pressure varies with the central aortic pressure and it is therefore convenient to normalize these values by dividing the ankle pressure by the brachial blood pressure. This ratio is referred to as ABI (ZIERLER ET AL. 2005).

$ABI \leq 0.9$ is considered indicative of the presence of PAD. The ABI values are considered mildly to moderately diminished when they are between 0.41 and 0.9 and severely decreased when ≤ 0.4 (HIRSCH ET AL. 2006). With lowering ABI, the haemodynamic severity of the occlusive disease becomes greater (NORGREN ET AL. 2007).

ABI may be inaccurate if the tibial vessels at the ankle become non-compressible, as may occur in patients with diabetes. Falsely elevated ABI may also be encountered in patients with renal failure or in very elderly individuals. These patients typically have an $ABI > 1.4$. Despite the artificially elevated ABI, these patients may suffer from significant PAD. Therefore, additional non-invasive diagnostic testing (e.g., TP or pulse volume recording), should be performed for these patients if they have symptoms strongly suggestive of PAD (HIRSCH ET AL. 2006, NORGREN ET AL. 2007).

The ABI provides prognostic information about the patient's survival; ABI values < 0.9 and > 1.4 were demonstrated to be associated with increased all-cause and cardiovascular mortality in a retrospective cohort study,

The Strong Heart Study (SHS) by Resnick et al., including 4,393 American Indians (RESNICK ET AL. 2004A). These results have been further supported by later studies (ANKLE BRACHIAL INDEX COLLABORATION 2008, SUOMINEN ET AL. 2010). An analogous, U-shaped association seems to exist between ABI values and major amputation rates as well. In a retrospective, registry-based study by Marston et al., evaluating 142 conservatively treated patients presenting with an ischaemic ulceration, $ABI < 0.5$ seemed to be associated with an elevated risk of limb loss (MARSTON ET AL. 2006). On the other hand, falsely elevated ABI (> 1.4) was associated with a significant increase in the risk for leg amputation in a subgroup analysis of the SHS, which included 1,974 diabetic American Indians, and a similar association was also shown in a registry-based study by Silvestro et al., evaluating 299 patients with 325 critically ischaemic limbs (RESNICK ET AL. 2004B, SILVESTRO ET AL. 2006).

Toe pressure and the toe-brachial index

AP measurements fail to reflect the severity of peripheral ischaemia when there is extensive pedal or digital arterial disease or when the leg arteries have become non-compressible due to medial calcification. This problem may be obviated by measuring pressures at toe level where the vessels are seldom affected by calcification (RAMSEY ET AL. 1983).

TP is measured with a pneumatic cuff wrapped around the proximal phalanx of the first or second toe with a flow sensor applied distally. TP is normally approximately 30 mmHg less than the AP. The toe-brachial index (TBI) is yielded by dividing the toe pressure with brachial pressure. $TBI < 0.7$ is considered diagnostic of PAD (HIRSCH ET AL. 2006, NORGREN ET AL. 2007, ZIERLER ET AL. 2005).

Imaging techniques

The anatomic pattern of the disease is an important factor when considering the type

of procedure for revascularization. Sufficient inflow and outflow have to be confirmed before taking up invasive measures. Diagnostic accuracy is an important factor when choosing the imaging modality – however, potential adverse effects, contraindications, cost, local availability and experience should also be taken into account.

Heretofore digital subtraction angiography (DSA) has been the standard of reference in the evaluation of lower extremity arterial disease. It is an invasive procedure with substantial costs and a risk, although small, of complications (WAUGH ET AL. 1992). Non-invasive or minimally invasive techniques for anatomic assessment of the peripheral arteries that could replace DSA would therefore be desirable. Indeed, in recent years, non-invasive and thus potentially safer and more convenient imaging techniques have developed rapidly. As has happened already in many vascular units, the trend seems to be that the non-invasive modalities will largely replace DSA as the primary tool for planning and follow-up of revascularization, thus reserving DSA for targeted therapeutic use (INSKO ET AL. 2005, LAKSHMINARAYAN ET AL. 2009).

Digital subtraction angiography

DSA is regarded as the gold standard for interventional planning. It provides excellent resolution, and endovascular interventions can be performed in conjunction with it (AYERDI ET AL. 2005). However, DSA has several liabilities. It involves radiation exposure and risks of complication associated with the arterial puncture and catheter manipulation – i.e., bleeding from the puncture site, intra-arterial thrombosis and vessel perforation. DSA carries an approximately 0.7% risk of a complication that is severe enough to alter patient management and a 0.16% mortality risk (NORGREN ET AL. 2007).

The use of an iodinated contrast medium includes a risk of a severe contrast reaction

of about 0.1%. Iodinated contrast agents are also associated with potential nephrotoxicity, and patients at increased risk of contrast nephropathy are those with baseline renal dysfunction, low cardiac output, dehydration or diabetes (HIRSCH ET AL. 2006, NORGREN ET AL. 2007). For patients at risk, vigorous hydration before contrast administration may prevent the deterioration of renal function (HIRSCH ET AL. 2006). The occurrence of nephrotoxicity appears to be dose-dependent, and therefore the amount of contrast medium used should be kept at minimum (HIRSCH ET AL. 2006).

If iodinated contrast medium is contraindicated, it is possible to use either carbon dioxide (CO₂) or gadolinium to opacify the arteries for angiography. However, with the use of CO₂ the image quality is inferior to that obtained with the use of an iodinated contrast medium (AYERDI ET AL. 2005). Nephrotoxicity is also a potential issue with gadolinium, as it has been shown to cause acute renal failure in patients with underlying chronic renal insufficiency on rare occasions (SAM ET AL. 2003). Gadolinium administration for patients with renal dysfunction has also been associated with a rare, but severe and potentially lethal condition, namely nephrogenic systemic fibrosis (NSF) (PENFIELD ET AL. 2007).

Colour-assisted duplex ultrasonography

In expert hands, colour-assisted duplex ultrasonography (DD) can provide most of the essential information of the anatomic location and degree of the arterial stenosis, but the crural arteries are challenging to image in their entirety (HIRSCH ET AL. 2006, NORGREN ET AL. 2007). DD is completely safe and a widely accessible method for vascular imaging, and the cost is rather low as compared to other modalities. DD is highly dependent on technical skill and thus susceptible to inter-observer variation (NORGREN ET AL. 2007, UBBINK ET AL. 2001). The accuracy of DD may be diminished, for example, due

to calcifications, obesity or oedematous soft tissues that obscure the visibility of the arteries (EIBERG ET AL. 2010).

Irrespective of the degree of ischaemia, the agreement between DSA and DD seems to be rather good in the femoropopliteal arteries, but is poorer in the infrapopliteal areas (FAVARETTO ET AL. 2007, EIBERG ET AL. 2010). The specificity of DD for detecting significant stenoses or occlusions seems high, although its sensitivity seems to be lower and also inferior to both magnetic resonance angiography (MRA) and computed tomography angiography (CTA) (COLLINS ET AL. 2007, FAVARETTO ET AL. 2007, LÖFBERG ET AL. 2001, VISSER AND HUNINK 2000). Despite this, a prospective controlled study on 114 patients by Koelemay et al. showed that in a vascular unit with wide expertise in DD, the management of patients with severe leg ischaemia could be based on DD in most patients without negative effects on clinical outcome, when compared to the control group within 30 days and at 2 years' follow-up (KOELEMAY ET AL. 2001B).

Magnetic resonance angiography

In many centres, three-dimensional gadolinium-enhanced (3D-Gd) MRA is the preferred method for imaging the peripheral vasculature (LAKSHMINARAYAN ET AL. 2009, NORGREN ET AL. 2007). MRA has become an accepted standard of evaluation for PAD, for it is minimally invasive and has been demonstrated to be highly accurate (COLLINS ET AL. 2007, KOELEMAY ET AL. 2001A, STEFFENS ET AL. 2003). A systematic review by Collins et al. including 58 studies on diagnostic accuracy and a meta-analysis by Visser and Hunink suggests that the sensitivity of MRA to detect PAD is superior to DD (COLLINS ET AL. 2007, VISSER AND HUNINK 2000). A prospective study by Langer et al. compared MRA and DSA in a series of 29 CLI patients and indicated that MRA may be better at detecting pedal bypass target arteries (LANGER ET

AL. 2009). An additional advantage of MRA lies in its 3D properties that may allow superior spatial depiction of eccentric or complex stenoses (LAKSHMINARAYAN ET AL. 2009, NORGREN ET AL. 2007).

Early venous enhancement due to fast arterial flow and venous shunting may be a problem when imaging infrapopliteal vessels with MRA in patients with CLI, cellulitis, ulceration or diabetes (FOO ET AL. 2001, LAPEYRE ET AL. 2005, PRINCE ET AL. 2002). In such cases, hybrid protocols, focusing separately on supragenicular and infragenicular arteries, have been utilized with good results (LAPEYRE ET AL. 2005, OWEN ET AL. 2009, PERELES ET AL. 2006).

MRA has unique limitations. It tends to overestimate the degree of stenosis due to a loss of signal caused by turbulent blood flow and, furthermore, vessel wall calcifications cannot be evaluated with it (LEE ET AL. 2000). Moreover, susceptibility artefacts arising from metallic stents, joint prostheses and surgical clips can cause signal loss within a vessel that mimics stenosis or occlusion (BARTELS ET AL. 2001, LEE ET AL. 2000, LENTHART ET AL. 2000). Indeed, assessing stent patency and in-stent restenosis is yet an unsolved challenge with MRA (LAKSHMINARAYAN ET AL. 2009).

The high-strength magnetic field utilized in MRA excludes patients with implanted metallic devices such as cardiac pacemakers, spinal cord stimulators and cochlear implants (HIRSCH ET AL. 2006, NORGREN ET AL. 2007). MRA may also be impossible to perform on patients with claustrophobia or co-operation problems, for the patient has to lay still for several minutes for imaging. Furthermore, as nephrotoxicity and NSF are potential issues with gadolinium, caution is advised when administering it for patients with chronic renal insufficiency (PENFIELD ET AL. 2007, SAM ET AL. 2003).

Computed tomography angiography

Multi-detector row CTA has been shown to be accurate in diagnostic imaging of

TABLE 4

The arterial segments to which the Bollinger scoring system is applied

1 Abdominal aorta	6 A. femoralis superficialis
2 A. iliaca communis	7 A. poplitea
3 A. iliaca externa	8 A. tibialis anterior
4 A. iliaca interna	9 A. fibularis
5 A. femoralis profunda	10 A. tibialis posterior

PAD, which was demonstrated in, for instance, the meta-analysis by Met et al. including 20 studies with a total of 957 patients (HEIJENBROK-KAL ET AL. 2007, MET ET AL. 2009). In a randomized controlled trial by Kock et al., 145 patients with PAD were assigned for CTA or DSA as the initial imaging modality, and CTA seemed to provide sufficient data for clinical decision making (KOCK ET AL. 2005). The specificity and sensitivity of CTA for the detection of a stenosis of >50% in a lower limb vessel are approaching those of MRA (COLLINS ET AL. 2007, OUWENDIJK ET AL. 2005, MET ET AL. 2009). The advantages of CTA are the relatively short imaging time and lower cost compared to MRA and DSA (OUWENDIJK ET AL. 2005, OUWENDIJK ET AL. 2006). The sensitivity for the detection of PAD seems to be better with CTA than DD (COLLINS ET AL. 2007).

Vessel wall calcifications have been reported to be the main reason for the misinterpretation of CT angiograms (OFER ET AL. 2003, OTA ET AL. 2004). Especially in small-calibre arteries, the presence of extensive vessel wall calcifications makes the production of interpretable maximum intensity projection images difficult, rendering the accuracy of CTA moderate in the calf and largely insufficient in calcified pedal arteries (KAU ET AL. 2011, OUWENDIJK ET AL. 2006). Additional disadvantages of CTA include the use of ionizing radiation, the use of po-

tentially nephrotoxic iodinated contrast media, and the time-consuming three-dimensional reconstruction techniques (OUWENDIJK ET AL. 2005).

Evaluation of arterial lesion severity and extent in infrainguinal PAD

The Bollinger scoring method

The Bollinger scoring method is a means of semi-quantitative description of a lower limb arterial angiogram (BOLLINGER ET AL. 1981). It was designed for a numerical evaluation of arterial occlusive disease progression or regression occurring either spontaneously or induced by treatment. In the scoring method, the infra-aortic arterial tree is divided into ten anatomical segments (Table 4), and each of the segments is scored separately according to the severity and extent of the disease (Table 5). Four categories of severity of the occlusive lesions are defined: 1) occlusion of the lumen, 2) stenosis >50% of the luminal diameter, 3) stenosis ≤50% but >25%, 4) plaques stenosing the lumen by ≤25%. Each type of lesion is further categorized by its extent: 1) single lesion, 2) multiple lesions affecting half of the segment or less, 3) multiple lesions affecting more than half of the segment (Table 5). The numbers appearing in the single fields of the scoring matrix correspond to score numbers. The additive score is obtained when the individual scores for the different categories of severity are summed in accordance with the following rules: 1) in the presence of oc-

TABLE 5

The Bollinger scoring matrix (MODIFIED FROM BOLLINGER ET AL. 1981)

	Severity			
	Stenosis	Stenosis	Plaque	
Occlusion	> 50 %	≤ 50 %	≤ 25 %	Extent of disease
	4	2	1	Single lesion
13	5	3	2	Multiple lesions affecting half of the segment or less
15	6	4	3	Multiple lesions affecting more than half of the segment
				: vectorial score

° The vertical columns represent the different severities of atherosclerotic lesions defined.

° The rows represent the extent of disease observed in each segment.

° The numbers appearing in the single fields correspond to score numbers and in practical work the fields chosen are marked with a cross and the additive score is then obtained by summing the numbers marked.

° The vectorial score is obtained by writing the numbers crossed below the vertical columns.

clusions, plaques or stenoses are not considered; 2) when both severities of stenoses (>50% and ≤50%) are present, plaques (≤25%) are not scored; 3) for each type of occlusive lesion only one extent category is scored. Additionally, in follow-up studies changes in occlusion length are taken into account – an increase or decrease in the occlusion length of 2 cm adds or diminishes the score by 1 point, respectively.

A vectorial score that describes the pattern of the occlusive process can also be calculated with the Bollinger matrix (Table 5). The different lesions are coded by their respective numbers appearing in the vertical columns. A complete occlusion involving not more than half of the segment is indicated in the column for occlusions by the number three (3) and a longer occlusion by the number five (5). If no number is marked in a column, the number zero (0) indicates that there is no lesion of this severity.

TASC

The first TASC document on the management of PAD was published in January 2000 as a result of cooperation between fourteen medical and surgical vascular, cardiovascular, vascular radiology and cardiology societies in Europe and North America (HIRSCH ET AL. 2006). This comprehensive report included morphological stratifications for femoropopliteal and infrapopliteal arterial lesions and recommendations for their treatment strategy.

The classifications of different femoropopliteal and infrapopliteal arterial lesions according to TASC are depicted in Tables 6 and 7. This classification has been widely used to characterize trial populations and treated lesions as well as to report the outcome of a specific intervention in lesions of different severity, allowing some comparisons to be made across studies.

Based on the evidence available at the time, the TASC Working Group recommended endovascular treatment as the

first-line strategy for lesions of type A and open surgery for lesions of type D, but declined to recommend initial treatment for type B and C lesions due to insufficient evidence.

TASC II

The TASC II document was published in 2007 and is an abbreviated update of the original TASC report focusing on key areas of diagnosis and management of PAD (NORGREN ET AL. 2007). Since the publication of TASC, advances in expertise in endovascular procedures had led to their common use even for TASC C and D lesions with satisfying outcomes (BLACK ET AL. 2005, DE-RUBERTIS ET AL. 2007). Hence, recommendations for treatment had become outdated and TASC II did include revised stratifica-

tions and revascularization recommendations for femoropopliteal arterial lesions (Figure 3). In general, in each TASC II lesion category, a more severe morphological form of disease is included than in the original TASC. Additionally, the TASC II type C category includes all new lesion types not characterized in TASC. In the TASC II document, endovascular therapy was recommended as the treatment of choice for type A lesions and bypass surgery for type D lesions. Furthermore, depending on co-morbidities, the patient's preferences and the local operator's long-term success rates, endovascular treatment was recommended as the preferred treatment for type B lesions and surgery for type C lesions. No revision was made to the TASC I classification of infrapopliteal lesions.

TABLE 6
TASC classification of femoropopliteal lesions (MODIFIED FROM DORMANDY ET AL. 2000)

Type A
• Single stenosis <3 cm
Type B
• Single stenosis 3–10 cm in length, not involving the distal popliteal artery
• Heavily calcified stenoses ≤3 cm in length
• Multiple lesions, each < cm (stenoses or occlusions)
• Single or multiple lesions in the absence of continuous tibial runoff to improve inflow for distal surgical bypass
Type C
• Single stenosis or occlusion >5 cm
• Multiple stenoses or occlusions, each 3–5 cm, with or without heavy calcification
Type D
• Complete common femoral artery or superficial femoral artery occlusions or complete popliteal and proximal trifurcation occlusions

Evaluation of outflow

One of the most important predictive technical factors of bypass graft failure is the outflow status of the distal arteries (ALBÄCK ET AL. 1998, BIANCARI ET AL. 1999A, PANAYITOPUOLOS ET AL. 1997). Its worsening has been shown to have a negative effect on the clinical success of infrainguinal endovascular interventions for CLI as well (BAKAL ET AL. 1990, DAVIES ET AL. 2008, FAGLIA ET AL. 2007). Ways of describing the outflow have therefore been searched for to determine a uniform scoring system that would aid in the decision-making when distal revascularization is planned. The presence of a completely open or only mildly stenosed outflow crural artery, particularly a tibial artery, has been shown to be associated with improved patency, leg salvage and survival after revascularization (BIANCA-

RI ET AL. 1999A, FAGLIA ET AL. 2007, PANAYITOPUOLOS ET AL. 1997).

Anatomical criteria to define the peripheral vascular runoff have been standardized by the 1997 revised Society for Vascular Surgery/International Society for Cardiovascular Surgery (SVS/ISCVS) runoff score (RUTHERFORD ET AL. 1997; **Tables 8 and 9**). The correlation of the runoff score with outcome after revascularization has been tested in numerous studies with mixed results (ALBÄCK ET AL. 1998, BIANCARI ET AL. 1999A, BIANCARI ET AL. 1999B, DAVIES ET AL. 2008, TAKOLANDER ET AL. 1995). However, no better scoring system has come along to replace it.

Treatment of CLI

The management of CLI requires a multidisciplinary team of experts in different ar-

TABLE 7
TASC classification of infrapopliteal lesions (MODIFIED FROM DORMANDY ET AL. 2000)

Type A
• Single stenoses <1 cm in the tibial or peroneal vessels
Type B
• Multiple focal stenoses of the tibial or peroneal vessels, each <1 cm in length
• 1 or 2 focal stenoses, each <1 cm long, at the tibial trifurcation
• Short tibial or peroneal stenosis in conjunction with femoropopliteal angioplasty
Type C
• Stenoses 1–4 cm in length
• Occlusions 1–2 cm in length of the tibial or peroneal vessels
• Extensive stenoses of the tibial trifurcation
Type D
• Tibial or peroneal occlusions >2 cm
• Diffusely diseased tibial or peroneal vessels

FIGURE 3

The TASC II classification of femoropopliteal arterial lesions.

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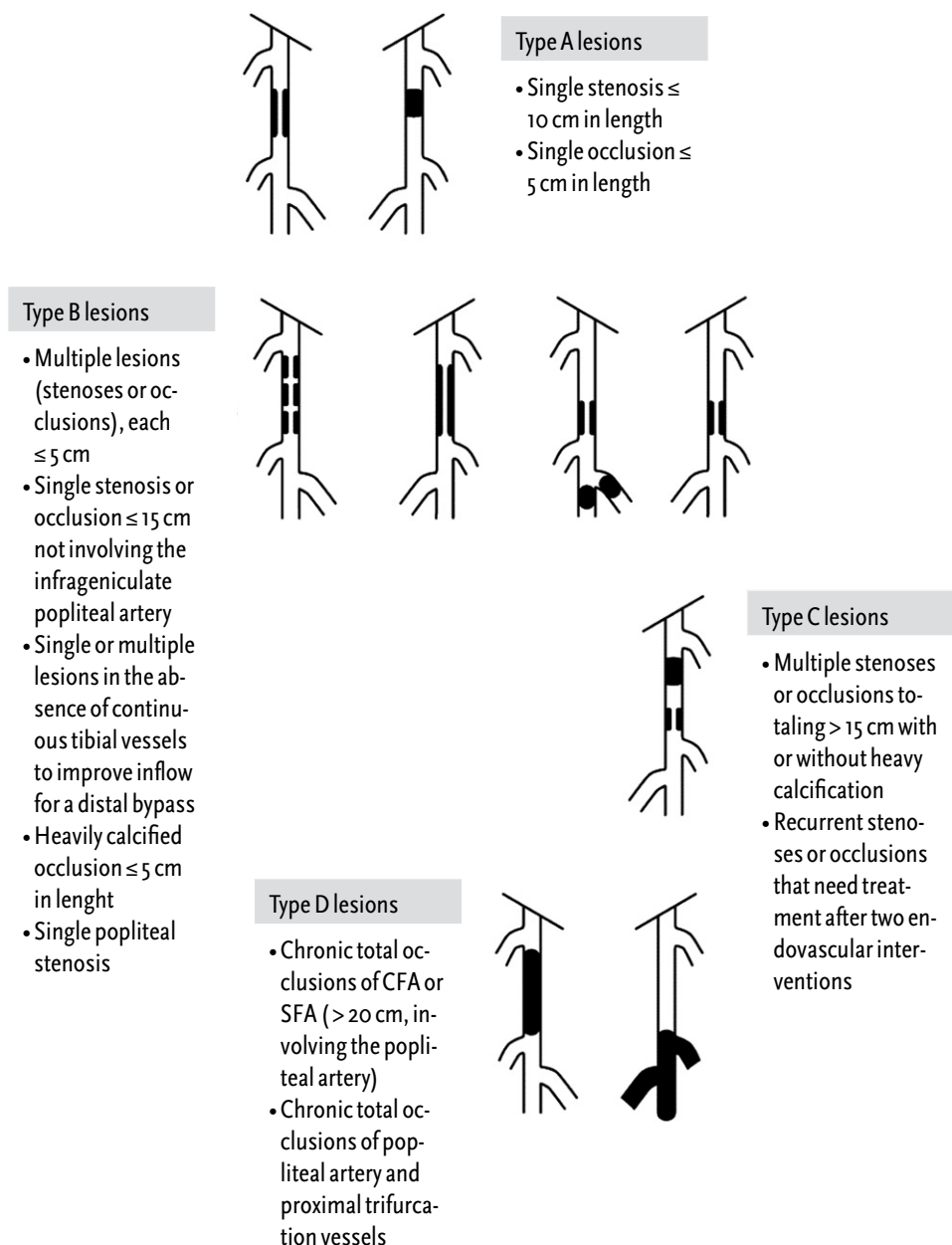
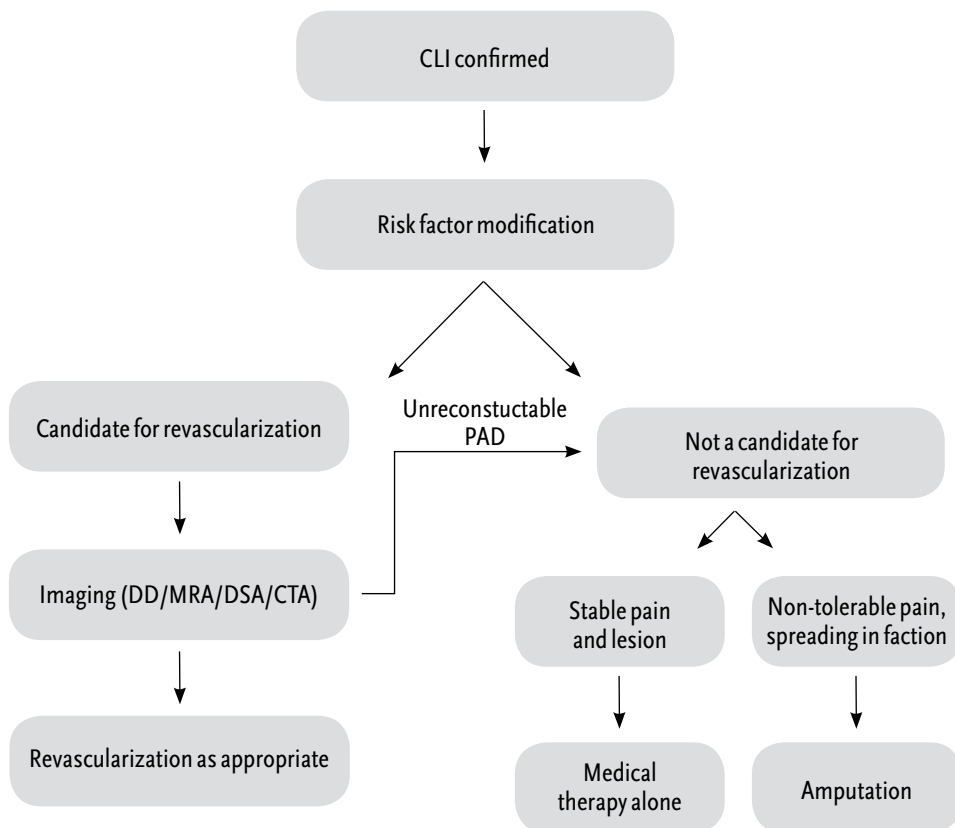


FIGURE 4

Algorithm for treatment of a CLI patient (MODIFIED FROM NORGRÉN ET AL. 2007).



eas of vascular disease (LUMSDEN ET AL. 2009, NORGRÉN ET AL. 2007). The goals of treating CLI are to relieve ischaemic pain, heal ischaemic ulcers, avoid limb loss, preserve mobility, improve the patient's functioning and quality of life, and prolong survival (NORGRÉN ET AL. 2007, VARU ET AL. 2010). Revascularization could optimally reach these goals. However, it might not be a viable option for a number of patients due to severe co-morbidities, short life-expectancy, non-ambulatory status or poor outflow vessels in the leg, and for these patients, conservative treatment or primary amputation might be the most appropriate choice of therapy

(Figure 4). Whichever form of therapy is chosen, the treatment of CLI should always include modification or elimination of atherosclerotic risk factors to slow down the progression of PAD and to reduce cardiovascular events, in addition to medical control of ischaemic symptoms and infection as well as optimization of cardiac and respiratory function (NORGRÉN ET AL. 2007).

Conservative treatment of CLI

Modification of atherosclerotic risk factors

Diabetes

It is unclear whether strict glycaemic control will protect peripheral circulation, improve cardiovascular outcomes or pre-

TABLE 8
Resistance values of runoff arteries according to SVS/ISCVS
(MODIFIED FROM RUTHERFORD ET AL. 1997)

	Degree of occlusion				
	3	2.5	2	1	0
Major runoff vessels	Occluded throughout the length	Occluded less than halfway of length; visible collaterals	50% to 99% greatest stenosis	20% to 49% greatest stenosis	Less than 20% greatest stenosis
Pedal runoff	No primary pedal artery patent	Partially patent or fully patent beyond critical in line occlusive lesion	In line continuity with patent out-flow vessel but incomplete arch	One or more subcritical stenoses distally but no in line	Fully patent pedal runoff (<20% stenosis)
Pedal arch	Little or no arch visualised	–	Diseased or partially occluded arch	Patent arch with no retrograde outflow	Completely patent arch connecting with retrograde flow-back into the other pedal artery

vent amputation (AMERICAN DIABETES ASSOCIATION, 2006). Nonetheless, it is associated with sustained decreased rates of retinopathy, nephropathy and neuropathy in diabetics (DCCT/EDIC RESEARCH GROUP 2000, UK PROSPECTIVE DIABETES STUDY [UKPDS] GROUP 1998). Additionally, a meta-analysis including 9,123 patients by Selvin et al. suggested that for every 1% point increase in haemoglobin A1C (HbA1c), there is a corresponding 26%–28% increase in the risk of PAD (SELVIN ET AL. 2004). The American Diabetes Association recommends HbA1c of <7% as the goal for the treatment of diabetic patients in general, but a level as close to nor-

mal (<6%) as possible without significant hypoglycaemia should be the target for the individual patient (AMERICAN DIABETES ASSOCIATION 2006).

Smoking cessation

For a patient with PAD the risk of death, cardiovascular events and amputation seems to be substantially greater in those individuals who smoke than in those who stop smoking (JONASON ET AL. 1987, FAULKNER ET AL. 1983, LEPÄNTALO ET AL. 1991). Smoking also has a negative effect on bypass graft patency, as continued smoking after lower limb bypass surgery was shown to result in a threefold increased risk of graft failure in a meta-analysis including 29 stud-

TABLE 9

Calculation of the SVS/ISCVS runoff score for infrainguinal revascularizations

(MODIFIED FROM RUTHERFORD ET AL. 1997)

Recipient artery	Runoff arterial segment	Resistance value		Weighting factor		Subscores		Total
Popliteal AK*	Popliteal		X	3	=		+1 =	runoff score
Popliteal BK	Anterior tibial		X	1	=			
	Posterior tibial		X	1	=			
	Peroneal		X	1	=			
						sum	+1 =	runoff score
Anterior tibial	Distal anterior tibial		X	2	=			
	Pedal arch		X	1	=			
						sum	+1 =	runoff score
Posterior tibial	Distal posterior tibial		X	2	=			
	Pedal arch		X	1	=			
						sum	+1 =	runoff score
Peroneal	Peroneal branches		X	1	=			
	Pedal arch		X	2	=			
						sum	+1 =	runoff score
Pedal	Pedal arch		X	3	=		+1 =	runoff score

*When calculating the runoff score for above-knee popliteal recipient artery, either popliteal above the knee (AK) or popliteal below the knee (BK) can be used, whichever offers the highest degree of resistance.

ies by Willigedael et al. (WILLIGEDAEL ET AL. 2005). A systematic review by Critchley et al. consisting of 20 studies with a total of 12,603 patients indicated that smoking cessation may have a greater effect on reducing the risk of mortality among patients with CAD who smoke than any other intervention or treatment (CRITCHLEY ET AL. 2003).

Consequently, the cessation of smoking is a cornerstone in the management of PAD at any stage.

Dyslipidaemia

A multicentre randomized controlled trial (RCT) with 20,536 patients, The Heart Protection Study (HPS), showed that the use of statins to lower LDL cholesterol has a protective effect in patients with PAD, as it re-

sulted in a 22% relative reduction in major cardiovascular events during the 5-year follow-up (HEART PROTECTION STUDY COLLABORATIVE GROUP 2000). Statin use also seems to reduce mortality in patients with CLI in particular; this was demonstrated by analyzing the cohort of The PProject of Ex-Vivo vein graft Engineering via Transfection (PREVENT III, PIII), a multicentre RCT comprising 1,404 CLI patients undergoing infrainguinal bypass surgery (SCHANZER ET AL. 2008A). For all symptomatic PAD patients, the target value for LDL is <2.5 mmol/l and <1.8 mmol/l for those with PAD and a history of vascular disease in other beds, i.e., CAD (HIRSCH ET AL. 2006). The target value for total cholesterol is <4.5 mmol/l (DEBACKER ET AL. 2003). No specific treatment goals were defined for HDL cholesterol or triglycerides, but concentrations of HDL cholesterol <1.0 mmol/l and fasting triglycerides >1.7 mmol/l, seem to serve as markers of increased cardiovascular risk (DEBACKER ET AL. 2003).

Hypertension

Hypertension is associated with a two to three-fold increased risk for PAD, and the treatment of high blood pressure prevents the occurrence of cardiovascular disease morbidity and mortality (CHOBANIAN ET AL. 2003, NORGREN ET AL. 2007, PSATY ET AL. 2003). The current recommendation is that blood pressure should be lowered at least to below <140/90 and even lower, if tolerated, in all hypertensive patients. Furthermore, a blood pressure level of <130/80 should be pursued, if the patient has diabetes, chronic renal disease or CVD and considered in patients with CAD (CHOBANIAN ET AL. 2003, MANCIA ET AL. 2007).

Antithrombotic therapy

The Antithrombotic Trialists' Collaboration (ATC) meta-analysis comprised 287 studies involving 135,000 patients in compar-

isons of antiplatelet therapy versus control and 77,000 in comparisons of different antiplatelet regimens, and it showed a significant reduction in MI, stroke and death with antiplatelet therapy in all patients with symptomatic cardiovascular disease. The study included a subset analysis on patients with PAD among whom a reduction of cardiovascular events was demonstrated with antiplatelet therapy (ANTITHROMBOTIC TRIALISTS' COLLABORATION 2002). According to current guidelines, lifelong aspirin therapy (75 to 325 mg/day) is recommended for all patients with PAD instead of no antiplatelet therapy (CLAGETT ET AL. 2004, NORGREN ET AL. 2007).

The TASC II document recommends antiplatelet therapy after an endovascular or surgical procedure and states further that it should be initiated preoperatively and continued as adjuvant pharmacotherapy indefinitely unless subsequently contraindicated (NORGREN ET AL. 2007). Aspirin is recommended for patients undergoing prosthetic infrainguinal bypass or PTA (CLAGETT ET AL. 2004). Warfarin is additionally an alternative for patients undergoing infrainguinal bypass with a venous graft, but this is accompanied by an increased risk of major bleeding episodes (DUTCH BYPASS ORAL ANTICOAGULANTS OR ASPIRIN (BOA) STUDY GROUP 2000, NORGREN ET AL. 2007). Direct thrombin inhibitors, such as dabigatran, are an emerging new group of anticoagulants that may be used as an alternative to warfarin (CONNOLLY ET AL. 2009). Clinical trials on their use in PAD are, however, still lacking.

The combination of aspirin and clopidogrel has been demonstrated to be superior to aspirin alone in preventing adverse cardiovascular events in patients undergoing percutaneous coronary intervention, patients with acute coronary syndromes without ST-segment elevation, and patients with ST-elevation MI (CHEN ET AL. 2005, MEHTA ET AL. 2001, YUSUF ET AL. 2001). This dual antiplatelet therapy is nowadays applied for at least

1 month after infrainguinal stent implantation in all major endovascular centres and ongoing stenting trials on the basis of data from the coronary field (SCHILLINGER ET AL. 2007). In the Clopidogrel and Acetylsalicylic Acid in Bypass Surgery for Peripheral Arterial Disease (CASPAR) study, a multicentre RCT with 851 patients, the same dual antiplatelet therapy was compared to aspirin alone in PAD patients undergoing bypass surgery, and no improvement in limb or systemic outcomes in the overall population was reached with the dual antiplatelet therapy. However, a post hoc subgroup analysis suggested that the dual antiplatelet therapy offered a benefit for patients receiving prosthetic grafts without significantly increasing major bleeding risk (BELCH ET AL. 2010).

Other medical and pharmacological treatment of CLI

Although some previous studies have suggested improved healing of ischaemic ulcers and reduction in amputation when treating CLI patients with prostanoids, their use have failed to modify the amputation rate in recent studies (BRASS ET AL. 2006, NORRGREN ET AL. 2007, UK SEVERE LIMB ISCHAEMIA STUDY GROUP 1991). The prediction of response to prostanoids is difficult, and they are rarely used in the treatment of CLI (NORRGREN ET AL. 2007).

Spinal cord stimulation (SCS) seems to be a possible treatment option for patients suffering from inoperable CLI. A meta-analysis of six controlled trials with 444 patients demonstrated a significant improvement in leg salvage for those CLI patients treated with SCS when compared to those treated with optimum medical treatment. In addition, patients treated with SCS required significantly fewer analgesics and showed a significant clinical improvement. The authors concluded, however, that the positive effects of SCS should be weighed against the high

cost and possible complications (UBBINK ET AL. 2006). SCS is not widely used for CLI.

Invasive treatment of CLI

Revascularization offers the best chance of leg salvage for CLI patients. Traditionally, bypass surgery with an autogenous vein has been considered the approach of choice to avoid amputation and is still regarded the gold standard for the treatment of CLI (HIRSCH ET AL. 2005, MILLS, 2005). However, bypass surgery is a demanding and potentially dangerous operation for the CLI patient, with a perioperative mortality rate ranging from 1% to 2% and postoperative wound complications affecting approximately 20% of the patients (NORRGREN ET AL. 2007, SLOVUT AND SULLIVAN, 2008). Therefore, the less invasive endovascular techniques, such as PTA, have gained acceptance as a treatment method for CLI in recent years. Although they perform inferiorly to bypass surgery in terms of patency, the leg salvage rates are comparable (ESKELINEN ET AL. 2005, FAGLIA ET AL. 2005, ROMITI ET AL. 2008; **Tables 10 and 11**). Indeed, in the past decade the number of endovascular interventions for leg salvage has increased dramatically (KUDO ET AL. 2006). The continuous improvement of endovascular techniques and devices has made more and more complex lesions amenable to the endovascular approach, and in some centres, the endovascular approach has even supplanted bypass surgery as the first-choice revascularization method (BARIL ET AL. 2010, HAIDER ET AL. 2006, KUDO ET AL. 2006).

Basic principles of infrainguinal revascularization

Bypass surgery

The surgical means of treating CLI is to create a bypass over the diseased, occluded arterial segment. Prior to the operation, unimpeded proximal arterial inflow must be ensured. Thereafter, the take-off level of the bypass graft (i.e., common femoral artery, superficial femoral artery [SFA] or popliteal ar-

TABLE 10

Leg salvage rates after infrainguinal revascularization for CLI

Author	Study	N	Leg salvage % (\pm SE)				B: vein graft
	type		1 year	3 years	5 years	10 years	E: stent
Conte et al. 2006	PM	1404	88 (-)	–	–	–	B: 100%
Pomposelli et al. 2003	RS	1032	–	–	78 (-)	58 (-)	B: 99.8%
Söderström et al. 2010	RS	636	83 (2)	80 (3)	76 (2)	–	B: 90%
Kudo et al. 2006	RS	75	–	–	74 (-)	–	B: 59%
Biancari et al. 1999a	RS	77	80 (-)	76 (-)	–	–	B: 15%
Jämsén et al. 2002	PS	116	68 (5)	65 (5)	60 (6)	–	E: None
Kudo et al. 2006	RS	105	–	–	91 (-)	–	E: 2%
Conrad et al. 2011	RS	447	88 (2)	84 (2)	74 (4)	–	E: 26%
Söder et al. 2000	PS	72	80 (5)	–	–	–	E: None
Scott et al. 2008	RS	265	88 (2.5)	75 (5.9)	–	–	E: 20%
Eskelinen et al. 2005	RS	230	92 (-)	–	–	–	E: 2%

M=multicentre; S=single centre; R=retrospective; P=prospective; N=number of limbs;
B=bypass; E=endovascular

tery) does not seem to correlate with patency (NORGREN ET AL. 2007). The good quality of the outflow artery is also an important determinant of patency, whereas the level of distal anastomosis is of lesser importance. In general, the the most proximal artery providing continous runoff to the foot should be selected as the primary target (CONTE 2010B, NORGREN ET AL. 2007).

The type of conduit is an important factor affecting the success of infrainguinal bypass surgery. The great saphenous vein (GSV) is considered the most durable conduit for infrainguinal revascularization. Alternative (i.e., arm veins or the lesser saphenous vein) and spliced vein grafts have been shown to perform inferiorly to single-segment GSV (FARIES ET AL. 2000, LONDREY ET AL. 1994). How-

ever, all vein grafts fare significantly better in comparison to prosthetic grafts, especially when the revascularization extends infra-genicularly (KLINKERT ET AL. 2003, NORGREN ET AL. 2007, PEREIRA ET AL. 2006).

The vein graft may be implanted in a reversed, non-reversed or in-situ bypass fashion, which produce comparable patency rates (BELKIN ET AL. 1996, SHAH ET AL. 1995, TAYLOR ET AL. 1990). In some circumstances, it may be advantageous to select one configuration over the other – i.e., to optimize artery-vein size match.

Endovascular revascularization

PTA is the traditional means of infrainguinal endovascular revascularization. A contralateral retrograde or an ipsilateral ante-grade femoral access are most commonly used. The arterial lesion is crossed with a

guidewire, and a balloon is inflated to dilate the stenosed/occluded arterial segment. Heparinization during the intervention is standard treatment (NORGREN ET AL. 2007).

The severity of limb ischaemia and the outflow status of distal arteries affect the outcome of PTA (DAVIES ET AL. 2008). Furthermore, the lesion complexity (i.e., lesion length, stenosis vs. occlusion and TASC II classification) and multilevel interventions have been shown to affect the outcome of endovascular interventions (DERUBERTIS ET AL. 2007, LAZARIS ET AL. 2006).

TASC II recommends stent placement when PTA of a SFA lesion fails acutely (NOR-

GREN ET AL. 2007). Even though there are promising intermediate-term results from primary stenting of SFA lesions, the current data does not support routine stenting over selective stenting (KASAPIS ET AL. 2009, SCHILLINGER ET AL. 2006, TWINE ET AL. 2009). There are many emerging catheter-based technologies such as laser atherectomy, drug-eluting balloons and drug-eluting stents (DUDA ET AL. 2006, LAIRD ET AL. 2006, ZELLER ET AL. 2011). Their role in the treatment of CLI is not yet established.

On choosing the revascularization strategy for CLI

There is no uniform treatment algorithm for CLI, and controversy prevails in regard

TABLE 11

Meta-analysis results of crural PTA and popliteal-to-distal bypass

(MODIFIED FROM ROMITI ET AL. 2008).

Result	1 month	6 months	1 year	2 years	3 years
Primary patency					
PTA	77.4 ± 4.1	65.0 ± 7.0	58.1 ± 4.6	51.3 ± 6.6	48.6 ± 8.0
Bypass	93.3 ± 1.1	85.8 ± 2.1	81.5 ± 2.0	76.8 ± 2.3	72.3 ± 2.7
<i>p-value</i>	<0.05	<0.05	<0.05	<0.05	<0.05
Secondary patency					
PTA	83.3 ± 1.4	73.8 ± 7.1	68.2 ± 5.9	63.5 ± 8.1	62.9 ± 11.0
Bypass	94.9 ± 1.0	89.3 ± 1.6	85.9 ± 1.9	81.6 ± 2.3	76.7 ± 2.9
<i>p-value</i>	<0.05	<0.05	<0.05		
Leg salvage					
PTA	93.4 ± 2.3	88.2 ± 4.4	86.0 ± 2.7	83.8 ± 3.3	82.4 ± 3.4
Bypass	95.1 ± 1.2	90.9 ± 1.9	88.5 ± 2.2	85.2 ± 2.5	82.3 ± 3.0
Survival					
PTA	98.2 ± 0.7	92.3 ± 5.5	87.0 ± 2.1	74.3 ± 3.7	68.4 ± 5.5
Bypass	NA	NA	NA	NA	NA

NA, not available

Values are pooled estimate and standard error.

to whether the first-line revascularization strategy should be surgical or endovascular. There are numerous studies promoting the advantages of either strategy, but almost all of them are flawed due to, for instance, retrospective analysis, no randomization, a small number of patients or data derived from a single centre. In the TASC II document, previous outcome data were applied to identify the location and types of femoropopliteal arterial lesions best treated by endovascular or open approaches (NORGREN ET AL. 2007). These recommendations provided strong evidence only for the mildest and most severe disease patterns (type A and D lesions), but the choice of treatment strategy for managing type B and C lesions were still left essentially to the physician's preference.

At present there is only one large multi-centre RCT comparing the two revascularization methods – the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial, in which 452 patients presenting with severe leg ischaemia (SLI) due to infrainguinal disease were randomised to receive either bypass surgery or PTA as first-line treatment strategy (ADAM ET AL. 2005). The patients were included in this series on the basis of having clinical symptoms of chronic limb ischaemia (Rutherford categories 4–6, Fontaine stages III–IV) of presumed arterial aetiology, hence regardless of AP measurements. Therefore, the broader term SLI was used, as the objective pressure criteria recommended by, e.g., TASC were not utilized. In the short term, the PTA first-strategy was associated with significantly lower morbidity, initial cost and shorter hospital stay. On the other hand, in the long term after 2 years, there was a significant improvement in survival and a trend toward improved amputation-free survival (AFS) in favour of the surgery first-strategy. Overall, there was no significant difference in cost between the

two treatment strategies, as the re-intervention rate was higher after PTA. Neither was there a difference in the overall health-related quality of life (ADAM ET AL. 2005, BRADBURY ET AL. 2010A, BRADBURY ET AL. 2010B). Previous studies have suggested that attempted PTA does not jeopardize the chances of a subsequent bypass surgery; however, in the as-treated analysis of the BASIL trial, a reduced AFS was observed for those who underwent bypass surgery after failed PTA when compared to those who received bypass surgery as the initial therapy (BRADBURY ET AL. 2010B, RYER ET AL. 2006, SANDFORD ET AL. 2007). Furthermore, AFS was reduced for those who received a prosthetic graft when compared to those who received a venous graft among the patients who underwent bypass surgery as the initial treatment method (BRADBURY ET AL. 2010B).

Therefore, the results of the BASIL trial suggested that those CLI patients surviving ≥ 2 years, and with a useable vein, are probably better served by bypass surgery as the first-line strategy. Furthermore, the patients who are expected to live < 2 years or those without an available vein are probably better served by PTA as the first-line strategy.

Amputation

Major amputation is indicated in CLI patients when there is a life-threatening infection involving the ischaemic leg, when rest pain cannot be controlled, when extensive necrosis has destroyed the foot, or when the pattern of arterial disease is considered unsuitable for a revascularization attempt (NORGREN ET AL. 2007). Primary amputation should also be considered if the CLI patient has a very limited life expectancy, terminal illness, dementia, dependent living status or is chronically bed-ridden (BIANCARI ET AL. 2000, NEHLER ET AL. 2004, NORGREN ET AL. 2007, TAYLOR ET AL. 2009, VARU ET AL. 2009).

Secondary amputation is indicated when vascular intervention is no longer possible, when the limb deteriorates despite a patent

reconstruction, or where there is persistent infection despite reconstruction attempts (NORGREN ET AL. 2007).

Outcome prediction models

The outcome of reconstructed and unreconstructed CLI can be rather poor (ADAM ET AL. 2005, LEPÄNTALO ET AL. 1996). It has been suggested that lower limb revascularization is worth the endeavour if there is reasonable probability that the patient will remain alive with an intact index limb at 1 year (SECOND EUROPEAN CONSENSUS DOCUMENT 1991). Estimation of the risk of poor post-operative outcome is of great clinical and economical importance when invasive procedures for the treatment of CLI are being considered. It is evident that the nature of failed lower limb revascularization is largely multi-factorial, as during the last decades a number of risk factors associated with poor outcome have been identified. Outcome prediction models have been developed to, for instance, guide the clinician in deciding on the optimal revascularization method and identify the patients whose poor outcome estimates suggest a conservative approach (ARVELA ET AL. 2010, BIANCARI ET AL. 2007, BRADBURY ET AL. 2010D, SCHANZER ET AL. 2008B).

The Finnvasc risk score

The Finnvasc risk scoring method was originally developed to predict 30-day post-operative mortality and/or major lower limb amputation in patients undergoing infrainguinal surgical revascularization for CLI (BIANCARI ET AL. 2007). Since then, this method has been shown to be useful in the estimation of immediate and long-term post-procedural outcome of patients undergoing infrainguinal bypass surgery or PTA for CLI (ARVELA ET AL. 2010, KECHAGIAS ET AL. 2008).

The basis of this method was derived from the data on 3,925 CLI patients who underwent infrainguinal surgical revasculariza-

tion extracted from the Finnvasc Registry. The Finnvasc Registry was a nation-wide vascular registry to which 25 Finnish hospitals prospectively entered data on surgical procedures during 1991–1999 (SALENTIUS ET AL. 1992). In this model diabetes, CAD, gangrene and urgent operation are independent risk factors for adverse post-operative outcome. The risk score for each patient is the number of these risk factors present. There was a significant association between high scores and adverse immediate post-operative outcome, and this was particularly true for a risk score ≥ 3 (BIANCARI ET AL. 2007).

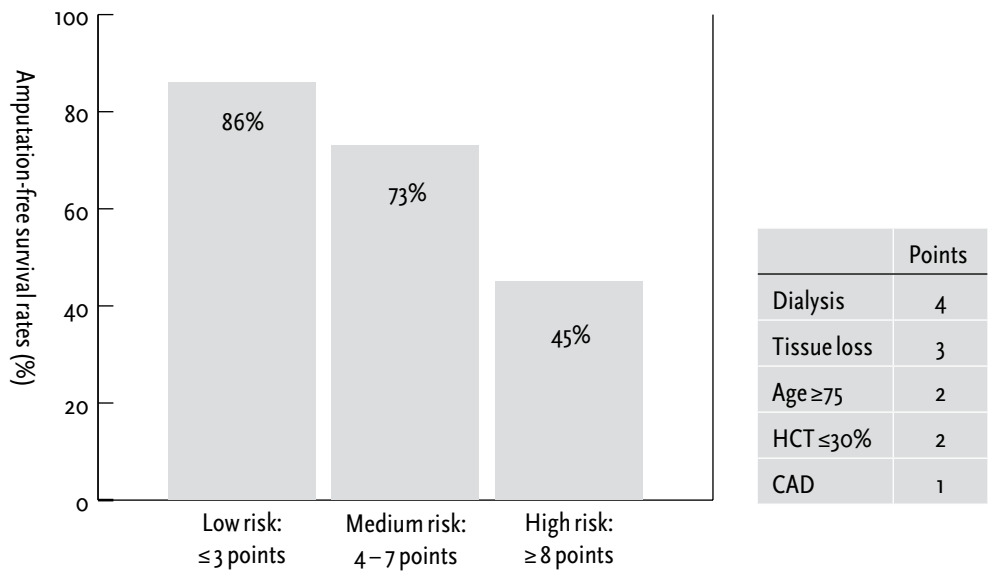
The PIII risk score

The PIII risk score can be used to estimate the 1-year AFS in CLI patients considered for infrainguinal revascularization (ARVELA ET AL. 2010, SCHANZER ET AL. 2008B, SCHANZER ET AL. 2009). This prediction model was derived from the cohort of patients who underwent open infrainguinal bypass surgery for CLI in the context of the PIII RCT (CONTE ET AL. 2005). In this model, points are assigned to each patient for the presence of dialysis (4 points), tissue loss (3 points), age ≥ 75 (2 points), anaemia (hematocrit ≤ 30 , 2 points) and advanced CAD (1 point), which were all found to be significant predictors of poor AFS at 1 year post-operatively. The PIII risk score is calculated by adding the yielded points together. On the basis of the score, the patients can be stratified in three risk categories: low (≤ 3 points), medium (4–7 points) and high (≥ 8 points; **Figure 5**).

The BASIL survival prediction model

The results from the BASIL trial suggest that CLI patients surviving >2 years are best served by bypass surgery as the first-line revascularization strategy rather than PTA (BRADBURY ET AL. 2010A). Accordingly, a survival prediction model was created to estimate the chances of survival >2 years (BRADBURY ET AL. 2010D). The 452 SLI patients who underwent infrainguinal revasculariza-

FIGURE 5
The PIII Score card (MODIFIED FROM SCHANZER ET AL. 2008)



tion in the context of the BASIL multicentre randomised trial formed the basis of this model. The factors that contributed to the Weibull predictive model were age, tissue loss, serum creatinine, number of AP measurements detectable, maximum AP measured, CAD, CVD, below the knee Bollinger score, body mass index, and smoking status. The survival probability for each patient can be calculated on the BASIL trial website (<http://basiltrial.com>). 🐼

Aims of the study

1. To compare the outcomes of infrainguinal PTA and bypass surgery for CLI
2. To assess the predictors of poor outcome after infrainguinal PTA for CLI
3. To evaluate the reproducibility of the TASC II classification for femoropopliteal arterial lesions
4. To evaluate the communication between interventional radiologists and vascular surgeons when treating patients with CLI 🍀

Material and methods

45

The effectiveness of infrainguinal percutaneous transluminal angioplasty in the treatment of critical limb ischaemia

Studies I–III

Patients and data collection

A total of 2,054 CLI patients underwent infrainguinal lower limb revascularization at the Helsinki University Central Hospital between 2000 and 2007. Data on these procedures were systematically collected in our institutional database (HUSVasc registry) and scrutinized retrospectively. Of these patients, 858 underwent unilateral femoropopliteal revascularization, constituting the study population of Study I. In this group, PTA was performed on 517 (60%) and bypass surgery on 341 (40%) patients.

The patient population of Study II was composed of the 1,023 CLI patients on whom unilateral revascularization extending into the infrapopliteal arteries was performed during the study period. Of them, 262 (26%) underwent PTA and 761 (74%) bypass surgery.

The patient population of Study III consisted of the 217 consecutive patients with 240 chronic critically ischaemic limbs treated with infrainguinal PTA between January 2006 and December 2007.

The data recorded in our institutional database included preoperative patient data such as co-morbidities, risk factors for PAD, indication for the revascularization as well as ABI and/or TP measurements. Additionally, operative details – such as urgency of the procedure, procedure code and graft material as well as postoperative data concerning graft patency, clinical outcome and possible complications and re-interventions – were noted. Dates of death were retrieved from Finnish national registry (Statistics Finland). Data on late major lower amputations and re-interventions have been completed retrospectively from the files of the National Research and Development Centre for Health and Welfare.

Arterial lesions were classified according to the TASC II document. The angiographic status of the runoff vessels was determined at the site of angioplasty/distal anastomosis downward, and the run-off score was calculated according to the SVS/ISCVS criteria from the completion angiogram. In addition, angiographic runoff was categorized in terms of target vessel patency, also termed as in-line open continuation down to the pedal arteries (I and II).

All cases and angiographies were reviewed and discussed at the daily integrated vascular meetings of vascular surgeons and interventional radiologists for decision-making on the revascularization method.

Endovascular revascularization

All endovascular procedures were performed in accordance with general guidelines, and

PTA was the preferred method. Stents were placed selectively in cases with immediate unsatisfactory results. A stent was placed in 3% of the primary interventions in the study population of Studies I and III. No stents were placed in infrapopliteal arteries.

Surgical revascularization

Non-reversed vein grafts were mostly used. Because of the lack of suitable veins, a prosthetic graft had to be utilized in 21% of the patients in Study I and in 6% of the patients in Study II.

Antithrombotic regimen

After a successful endovascular intervention, the patients were put on dual antiplatelet therapy of clopidogrel and aspirin for at least 1 month, after which they were prescribed lifelong aspirin, with the exception of those who were already on continued anticoagulation before revascularization.

After bypass surgery, the patients received low molecular weight heparin during their post-operative hospital stay, in addition to aspirin which was continued indefinitely.

Follow-up

All patients were followed until their symptoms subsided and/or wounds healed. After endovascular revascularization, the routine follow-up consisted of one clinical examination and ABI measurement at one month after the procedure, whereas bypass surgery patients were followed by a clinical examination, ABI measurement and DD scan at 1, 6 and 12 months routinely. In the endovascularly treated patient group, a DD scan was performed only if necessitated by the clinical situation.

Outcome endpoints

In Studies I and II, overall survival, major lower limb amputation, (major) AFS, freedom from any further re-intervention (in-

cluding all open and endovascular re-interventions performed to maintain the original revascularization and redo-procedures performed due to occlusion of the original revascularization) and freedom from surgical re-intervention (redo-bypass, i.e., bypass that comprises more than half of the graft) were the main outcome measures.

In Study III, the primary outcome measures were death, (major) amputation and the need for secondary bypass surgery within 6 months after the primary endovascular procedure. The secondary outcome measures were the overall survival and (major) amputation rate, the overall need for secondary bypass surgery, the overall need for any re-intervention and the need for endovascular re-intervention.

Study IV

The study material consisted of 200 preprocedural angiograms of CLI patients undergoing a femoropopliteal endovascular intervention at the Helsinki University Central Hospital during 2005–2006.

During the first study phase, seven investigators (two senior vascular surgeons, two vascular surgical trainees, two angiologists and one angiologist in training) independently categorized the femoropopliteal lesions on the first 100 angiograms according to the TASC II document on hand. After this, two intervention sessions were carried out; the first was a discussion of the 25 most controversial cases by a panel of 22 vascular surgeons and vascular trainees, and in the second session the seven original investigators sought agreement on the TASC II classification philosophy and discussed the principles of categorizing those arterial lesions not directly belonging to any of the TASC II classes.

Thereafter, in the second phase of the study, the remaining 100 angiograms were evaluated by the same seven investigators in a manner similar to the first phase.

Study V

In 2007, a total of 351 patients with CLI were referred by vascular surgeons to the Department of Radiology for DSA or an endovascular procedure at the Helsinki University Central Hospital. These referrals were scrutinized retrospectively.

The quality of the referral was assessed for the adequacy of description of the patient's clinical situation. This was evaluated by recording whether the referral text included the indication for the DSA, pulse palpation status, ABI and/or TP measurements. Data were gathered on whether the clinician wished for 1) DSA only, 2) endovascular intervention to treat a lesion on the basis of other vascular imaging or 3) DSA, and in case of a suitable arterial lesion, additionally an endovascular intervention.

On the other hand, the execution of this request by the interventional radiologist was evaluated. If the request and execution differed from each other, the reason for this was recorded as well as whether a vascular surgeon was a co-operator in the procedure or had been consulted prior to the intervention.

Statistical methods

In all studies, except for Study IV, the data were statistically analyzed using SPSS (Statistical Package for Social Sciences, SPSS Inc, Chicago, IL, USA) software.

In Studies I and II, propensity score analysis was used to reduce bias when calculating the effect of the treatment. Pearson's chi square test, Fisher exact test and Mann-Whitney test were used for univariate analysis. Logistic regression with backward selection was performed to calculate the risk, the so-called propensity score, of the patients to be included either in the PTA or bypass surgery group. Hosmer-Lemeshow's test was used to assess the regression model fit. Variables having a $p < 0.2$ at univariate analysis

were included in the regression model. Receiver operating characteristic (ROC) curve analysis was used for estimation of the area under the curve of the model predicting the probability of being included into the PTA or bypass surgery group.

The calculated propensity score was used for risk adjustment in multivariable analysis and for one-to-one matching. One-to-one propensity score matching between study groups was done according to a difference in the propensity score of < 0.005 . Cox regression with the help of backward selection was used to adjust the effect of treatment method on propensity score as well as other variables in evaluating continuous outcome endpoints. Long-term outcome was assessed by the Kaplan-Meier's method with the log-rank test and the Cox regression method. Outcome in the propensity-matched pairs was evaluated by Kaplan-Meier's methods as well as the Cox regression method. A $p < 0.05$ was considered statistically significant.

In Study III, the predictors of primary and secondary endpoints were identified with a univariate screen using $p < 0.2$ as a threshold for inclusion in the multivariate analyses. A Cox regression model with enter selection was used in the multivariate analysis for the outcome endpoint measures. Kaplan-Meier survival curves were utilized to describe the differences in survival with associated factors.

In Study IV, a multi-observer variation of Brennan and Brediger's free marginal kappa (κ_{free}) was used to calculate a change-adjusted measure of agreement using the Online Kappa Calculator (www.justusrandolph.net/kappa). Values of κ_{free} can range from -1.0 to 1.0, with -1.0 indicating perfect disagreement below chance, 0.0 indicating agreement equal to chance and 1.0 indicating perfect agreement above chance. A κ_{free} of 0.70 or above was considered to indicate adequate inter-observer agreement.

In Study V, Chi-square test was used to test statistical significance. ☛

Results

Studies I and II

The overall patient series

The baseline clinical characteristics and operative data of the study populations are given in **Table 12**. The mean length of follow-up was 2.6 ± 2.2 years.

Study I. The leg salvage rates of the overall population at 30-day, 1-year, 3-year and 5-year intervals were 98.0%, 90.1%, 85.9% and 83.3%, respectively. At the same intervals, the respective survival rates were 96.8%, 78.2%, 61.2% and 52.2%, and the respective AFS rates were 94.4%, 73.9%, 55.6% and 46.3%. Further revascularization procedures were required for 111 (21.5%) patients in the PTA group and for 63 (18.5%) patients in the bypass surgery group.

Study II. Leg salvage rates of the overall population at 30-day, 1-year, 3-year and 5-year intervals were 94.4%, 83.0%, 78.9% and 75.9%, respectively. At the same intervals, the respective survival rates were 94.8%, 75.1%, 56.3% and 44.1%, and the respective AFS rates were 90.1%, 65.6%, 47.8% and 37.2%. Further revascularization procedures were required for 48 (18.3%) patients in the PTA group and for 159 (20.9%) patients in the bypass surgery group.

PTA versus bypass surgery in the overall patient series

PTA had poorer long-term results than bypass surgery in the femoropopliteal segment; there was a significant difference in survival (49.2% vs. 57.1%, $p=0.048$), AFS (42.0% vs. 53.7%, $p=0.003$) and leg salvage (78.2% vs. 91.8%, $p<0.0001$) at 5 years in favour of the bypass surgery group. On the other hand, the long-term results achieved with PTA and bypass surgery extending to the infrapopliteal

TABLE 12
Patient characteristics and procedural data

	Study I		Study II		Study III	
	PTA	Bypass surgery	PTA	Bypass surgery	PTA	PTA
	517 patients	341 patients	262 patients	761 patients	217 patients with 240 critically ischaemic limbs	
Age (years)	74.5±11.8	71.5±10.4	74.5±11.4	73.6±11.2	0.18	74.6±11.4
Female	201 (38.9)	173 (50.7)	158 (60.3)	431 (56.6)	0.30	119 (54.8)
Diabetes mellitus	301 (58.2)	137 (40.2)	194 (74.0)	417 (54.8)	<0.0001	163 (75.1)
Cardiac morbidity	318 (61.5)	207 (60.9)	174 (66.4)	492 (64.7)	0.64	151 (69.6)
Hypertension	394 (76.4)	237 (69.9)	204 (77.9)	557 (73.2)	0.14	201 (92.6)
Hyperlipidaemia			116 (44.3)	286 (37.6)	0.07	119 (54.8)
Cerebrovascular disease	110 (21.3)	45 (13.4)	63 (24.0)	135 (17.7)	0.03	51 (23.5)
Pulmonary disease	78 (15.1)	73 (21.4)	41 (15.6)	86 (11.3)	0.07	42 (19.4)
Smoking	122 (23.6)	127 (37.7)	32 (12.2)	163 (21.4)	0.001	28 (12.9)
Previous lower limb revascularization	61 (11.8)	56 (16.4)	23 (8.8)	145 (19.1)	<0.001	-
Previous revascularization of the same segment	45 (8.7)	30 (8.8)	10 (3.8)	78 (10.2)	0.001	18 (7.5)
Serum creatinine (μmol/L)	145±149	106±90	143±140	123±124	0.001	148 (38–1114)
eGFR (mL/min/1.73 m2)	62±34	75±34	62±31	70±34	0.001	-
CKD classes:	1	95 (18.4)	93 (27.3)	185 (24.3)	0.04	-
	2	159 (30.8)	136 (39.9)	267 (35.1)		-
	3	175 (33.8)	87 (25.5)	88 (33.6)		-
	4	42 (8.1)	15 (4.4)	18 (6.9)		-
	5	46 (8.9)	10 (2.9)	20 (7.6)		-

Indication for revascularization									
Rest pain (Fontaine III)	103 (19.9)	149 (43.7)			17 (6.5)	206 (27.1)		<0.001	16 (6.7)
Ulcer (Fontaine IV)	334 (64.6)	171 (50.1)			199 (76.0)	438 (57.6)			157 (65.4)
Gangrene (Fontaine IV)	80 (15.5)	21 (6.2)			46 (17.6)	117 (15.4)			67 (27.9)
Runoff score	6.7±2.3	5.5±2.3			6.9±1.7	6.9±2.5		0.47	6.8±2.0
Target vessel patent down to the pedal arteries	276 (53.4)	257 (75.4)			136 (51.9)	622 (81.7)		<0.001	116 (48.3)
Most distal target artery (Studies I and III)									
Superficial femoral artery (Study III)	-	-			-	-			68 (28.3)
Popliteal artery (Study III)	-	-			-	-			64 (26.7)
Below the knee popliteal artery (Study I)	91 (17.6)	233 (68.3)			-	-			-
Target level (Study II)	-	-						<0.001	
Crural arteries	-	-			260 (99.2)	584 (76.7)			108 (45)
Foot arteries	-	-			2 (0.8)	177 (23.3)			-
Bypass graft									
Vein graft	-	263 (78.7)			-	717 (94.2)			-
Prosthetic graft		71 (21.3)			-	44 (5.8)			

Numbers are n (%) unless otherwise stated
CKD classes: Chronic kidney disease classes according to estimated glomerular filtration rate (eGFR): class 1 (normal): eGFR ≥ 90;
class 2 (mild): eGFR 60–89; class 3 (moderate): eGFR 30–59; class 4 (severe): eGFR 15–29; class 5 (kidney failure) eGFR <15

segment were similar in both treatment groups in terms of survival, AFS and leg salvage (Table 13).

Freedom from any re-intervention did not differ between the PTA and bypass surgery group infrainguinally, but freedom from surgical re-intervention was significantly lower after PTA at 5 years (Table 13).

The propensity score analysis

Patients treated with PTA had more co-morbidities compared to those treated with bypass surgery. In both Studies I and II, the patients in the PTA group were significantly more likely to have diabetes and renal insufficiency. The status of the run-off vessels was also significantly poorer in the PTA group in both studies; the PTA patients had less frequently a patent target vessel down to the pedal arteries and, additionally, in Study I the runoff-score was worse compared to the bypass surgery group.

As the study groups differed markedly from each other in their observed covariates, the propensity score was calculated to estimate the risk of these patients to undergo either PTA or bypass surgery. Variables included in the logistic regression model for the calculation of the propensity score in Study I were age, sex, diabetes, cerebrovascular disease, pulmonary disease, smoking, previous lower limb revascularization, chronic kidney disease class according to estimated glomerular filtration rate (eGFR), tissue loss, runoff score and patent target vessel down to the pedal arteries. In Study II, these were age, diabetes, hypertension, hyperlipidemia, cerebrovascular disease, pulmonary disease, smoking, previous revascularization of the same arterial segment, eGFR, indication for revascularization, patent target vessel down to the pedal arteries and procedure target level.

The obtained propensity score had an area under the ROC curve of 0.73 (95% con-

fidence interval (CI) 0.70–0.76, $p < 0.0001$) in Study I and 0.82 (95% CI 0.79–0.84, $p < 0.001$) in Study II.

PTA versus bypass surgery according to propensity score analysis

In the overall series, when treatment method was adjusted for propensity score, PTA was associated with significantly poorer leg salvage ($p = 0.020$, risk ratio (RR) 1.81, 95% CI 1.10–2.97) when the femoropopliteal segment was treated. However, when procedures extending to the infrapopliteal segment were performed, leg salvage did not differ significantly between the treatment groups ($p = 0.19$). There was no significant difference between the treatment groups in either study in terms of survival, AFS or freedom from any re-intervention when adjusted for propensity score. Nonetheless, in both studies freedom from surgical re-intervention was significantly lower for the PTA group.

One-to-one propensity score matching provided 241 pairs of patients in Study I and 208 pairs of patients in Study II who underwent either PTA or bypass surgery (Table 14). The late outcome estimates in the propensity score matched pairs are shown in Table 15.

During the five-year follow-up, PTA was associated with significantly poorer leg salvage in the matched-pairs analysis (74.3 % vs. 88.2%, $p = 0.031$) when the femoropopliteal level was treated, but no significant difference was observed in terms of leg salvage between the study groups when the infrapopliteal level was also treated (74.4% vs. 69.3% for PTA and bypass respectively, $p = 0.11$). However, PTA and bypass surgery achieved similar rates of survival, AFS and freedom from any re-intervention in the long term in both studies. In the matched-pairs analysis, the freedom from surgical re-intervention was significantly lower in the PTA group in both studies (at 5 years; Study I: 86.1% vs. 89.8%, $p = 0.025$; Study II: 85.3% vs. 91.4%, $p = 0.05$).

TABLE 13

Kaplan-Meier's estimates of late outcome in the overall series.

The number of patients entering intervals is reported in parentheses.

	Study I	5 years	<i>p</i> -value	Study II	5 years	<i>p</i> -value
Overall survival	PTA	49.2% (111)	0.048	PTA	47.5% (34)	0.53
	Bypass surgery	57.1% (57)		Bypass surgery	43.3% (129)	
Leg salvage	PTA	78.2% (96)	<0.0001	PTA	75.3% (25)	0.78
	Bypass surgery	91.8% (54)		Bypass surgery	76.0% (111)	
Amputation-free survival	PTA	42.0% (97)	0.003	PTA	37.7% (25)	0.81
	Bypass surgery	53.7% (54)		Bypass surgery	37.3% (111)	
Freedom from any re-intervention	PTA	75.2% (95)	0.3	PTA	77.3% (27)	0.47
	Bypass surgery	75.4% (39)		Bypass surgery	74.4% (89)	
Freedom from surgical re-intervention	PTA	85.7% (101)	<0.0001	PTA	86.2% (31)	<0.001
	Bypass surgery	91.5% (52)		Bypass surgery	94.3% (122)	

**PTA versus bypass surgery:
subgroup analysis (II)**

*Late outcome after isolated
infrapopliteal revascularization.*

Study II included 374 patients (36.6%) who underwent isolated infrapopliteal revascularization. PTA was performed on 198 patients and popliteodistal bypass surgery on 176 patients. In the overall series of this subgroup,

PTA was associated with significantly better leg salvage at 5 years (75.5% vs. 68.0%, $p=0.04$), but with significantly lower freedom from surgical re-intervention (86.3% vs. 95.9%, $p=0.001$). At 5 years, PTA and bypass surgery yielded similar results in terms of survival (47.2% vs. 39.5%, $p=0.27$), AFS (33.7% vs. 32.7%, $p=0.58$) and freedom from any re-intervention (78.8% vs. 85.2%, $p=0.17$).

The propensity score was calculated also for this subgroup of patients. Its area un-

TABLE 14

Patient characteristics and operative data for the one-to-one propensity score matched pairs

	Study I		Study II	
	PTA	Bypass surgery	PTA	Bypass surgery
	241 patients	241 patients	208 patients	208 patients
				<i>p</i> -value
Age (years)	74.3±11.8	72.7±10.2	74.3±11.3	73.7±11.0
Female	111 (46.1)	110 (45.6)	125 (60.1)	111 (53.4)
Diabetes mellitus	100 (41.5)	102 (42.3)	154 (74.0)	157 (75.5)
Cardiac morbidity	145 (60.2)	149 (61.8)	134 (64.4)	146 (70.2)
Hypertension	179 (74.3)	174 (72.5)	163 (78.4)	152 (73.1)
Hyperlipidaemia	-	-	90 (43.3)	76 (36.5)
Cerebrovascular disease	39 (16.2)	36 (14.9)	46 (22.1)	48 (23.1)
Pulmonary disease	40 (16.6)	39 (16.2)	23 (11.1)	20 (9.6)
Smoking	62 (25.7)	79 (32.9)	28 (13.5)	29 (13.9)
Previous lower limb revascularization	22 (9.1)	34 (14.1)	17 (8.2)	15 (7.2)
Previous revascularization of the same segment	16 (6.6)	16 (6.6)	8 (3.8)	5 (2.4)
Serum creatinine (μmol/L)	108±86	107±85	135±132	135±145
eGFR (mL/min/1.73 m ²)	71±32	72±35	64±31	65±30
CKD classes:	1	59 (24.9)	39 (18.8)	46 (22.1)
	2	91 (37.8)	89 (36.9)	69 (33.2)
	3	72 (29.9)	73 (30.3)	71 (34.1)
	4	11 (4.6)	13 (5.4)	9 (4.3)
	5	7 (2.9)	7 (2.9)	13 (6.3)

Indication for revascularization				0.25			0.45
Rest pain (Fontaine III)	63 (26.1)	64 (26.6)			15 (7.2)	13 (6.3)	
Ulcer (Fontaine IV)	148 (61.4)	158 (65.6)			158 (76.0)	150 (72.1)	
Gangrene (Fontaine IV)	30 (12.4)	19 (7.9)			35 (16.8)	45 (21.6)	
Runoff score	6.2±2.2	5.9±2.2		0.80	6.8±1.6	6.6±1.3	0.019
Target vessel patent down to the pedal arteries	164 (68.0)	165 (68.5)		0.92	122 (58.7)	122 (58.7)	1.00
Most distal target artery (Study I)							
Below the knee popliteal artery	44 (18.3)	165 (68.5)		<0.0001	-	-	
Target level (Study II)							1.00
Crural arteries	-	-			206 (99.0)	205 (98.6)	
Foot arteries	-	-			2 (1.0)	3 (1.4)	
Bypass graft							
Vein graft	-	194 (80.5)				198 (95.2)	
Prosthetic graft	-	47 (19.5)				10 (4.8)	

Numbers are n (%) unless otherwise stated
CKD classes: Chronic kidney disease classes according to estimated glomerular filtration rate (eGFR); class 1 (normal): eGFR ≥ 90; class 2 (mild): eGFR 60–89; class 3 (moderate): eGFR 30–59; class 4 (severe): eGFR 15–29; class 5 (kidney failure) eGFR <15

TABLE 15

Kaplan-Meier's estimates of late outcome in the propensity-score-matched pairs.
The number of patients entering intervals is reported in parentheses.

	Study I			Study II		
	241 pairs of patients	5 years	<i>p-value</i>	208 pairs of patients	5 years	<i>p-value</i>
Overall survival	PTA	53.4% (56)	0.85	PTA	46.2% (24)	0.44
	Bypass surgery	52.5% (39)		Bypass surgery	39.8% (38)	
Leg salvage	PTA	77.3% (48)	0.031	PTA	74.4% (17)	0.11
	Bypass surgery	88.2% (36)		Bypass surgery	69.3% (30)	
Amputation-free survival	PTA	44.6% (48)	0.54	PTA	36.9% (17)	0.26
	Bypass surgery	47.6% (36)		Bypass surgery	29.9% (30)	
Freedom from any re-intervention	PTA	74.5% (48)	0.13	PTA	76.6% (18)	0.17
	Bypass surgery	76.5% (29)		Bypass surgery	70.4% (23)	
Freedom from surgical re-intervention	PTA	86.1% (52)	0.025	PTA	85.3% (22)	0.045
	Bypass surgery	89.8% (35)		Bypass surgery	91.4% (35)	

der the ROC curve was 0.76 (95% CI 0.71–0.81, $p < 0.001$).

When adjusted for the propensity score, PTA was associated with better leg salvage at 5 years ($p = 0.04$), but with a lower freedom from surgical re-intervention ($p = 0.002$). The difference between the PTA and bypass sur-

gery groups was not statistically significant in terms of survival ($p = 0.27$), AFS ($p = 0.78$) or freedom from any re-intervention ($p = 0.17$).

One-to-one propensity score matching provided 89 pairs of patients who underwent an isolated infrapopliteal revascularization. Here, PTA tended to achieve better leg salvage at 5 years (79.2% vs. 68.6%, $p = 0.12$), but was associated with a lower free-

TABLE 16

Independent risk factors associated with overall mortality.

	HR (95% CI)	<i>p</i> -value
Age/year	1.03 (1.01–1.1)	0.005
Cardiac morbidity	2.3 (1.3–4.1)	0.003
Inability to ambulate	2.3 (1.4–4.0)	0.002
Renal insufficiency	2.6 (1.6–4.4)	0.000
Dyslipidaemia	0.5 (0.3–0.8)	0.006

HR=hazard ratio, CI=confidence interval

dom from surgical re-intervention (85.9% vs. 93.1%, $p=0.03$) when compared to bypass surgery. The difference between PTA and bypass surgery groups was not statistically significant at 5 years in terms of survival (38.9% vs. 35.6%, $p=0.89$), AFS (30.5% vs. 29.5%, $p=0.82$) or freedom from any re-intervention (82.1% vs. 84.0%, $p=0.60$).

Study III

The baseline clinical characteristics and procedural data of the study population are given in Table 12. A re-intervention was required for 58 (24%) legs. The most distal level treated was the femoropopliteal segment in 132 (55%) legs and interventions extending to infrapopliteal arteries were performed on 108 (45%) legs.

The mean follow-up was 17 months. AFS was 91%, 71%, 61% and 49% at 30 days, 6 months, 1 year and during the whole follow-up period, respectively. Leg salvage was 96%, 88%, 83% and 80% at 30 days, 6 months, 1 year and during the whole follow-up period, respectively. Fourteen percent of the patients had died, lost their leg or undergone secondary bypass surgery at 30 days post-procedurally and this figure was 37%, 48% and 58% at 6 months, 1 year and during the whole follow-up period.

Multivariate analysis of the primary outcome measures

In the multivariate analysis, the independent risk factors associated with death within 6 months after the primary procedure were age ($p=0.003$, hazard ratio (HR)=1.1; 95% CI 1.0–1.1), cardiac morbidity ($p=0.021$, HR=2.9; 95% CI 1.2–7.2), inability to ambulate upon hospital arrival ($p=0.006$, HR=3.0; 95% CI 1.4–6.5), and renal insufficiency ($p=0.008$, HR=2.5; 95% CI 1.3–5.0). Surprisingly, patients with a normal or mediasclerotic pre-procedural ABI (ABI ≥ 0.9) had the highest 6-month mortality when compared to those with a lowered (≤ 0.89) pre-procedural ABI. For instance, the patients whose pre-procedural ABI was in the range of 0.6–0.89 had a significantly lower mortality rate at 6 months when compared to those with a normal (0.9–1.29) pre-procedural ABI ($p=0.003$, HR=0.2; 95% CI 0.1–0.6).

The significant predictors of amputation within 6 months after the primary intervention were an urgent procedure ($p=0.022$, HR=2.8; 95% CI 1.2–6.5), the inability to ambulate upon hospital arrival ($p=0.001$, HR=4.3; 95% CI 1.9–10.2) and gangrene as the indication for the procedure ($p=0.023$, HR=2.9; 95% CI 1.2–7.3).

Compared to an ulcer, gangrene was significantly more strongly associated with amputation at 6 months ($p=0.023$, HR=3.0; 95% CI 1.2–7.8).

The only independent risk factor associated with the need for secondary bypass surgery within 6 months after the primary procedure was the inability to ambulate upon hospital arrival ($p=0.045$, $HR=2.7$; 95% CI 1.02–7.0).

Multivariate analysis of the secondary outcome measures

In the multivariate analysis, the independent risk factors associated with overall mortality were age, cardiac morbidity, the inability to ambulate upon hospital arrival and renal insufficiency. Dyslipidaemia had a protecting effect in regard to overall mortality. Table 16 summarizes the respective hazard ratios, confidence intervals and p -values.

The significant predictors of amputation during the whole follow-up period were an urgent procedure, the inability to ambulate upon hospital arrival, gangrene as the indication for the procedure and a mediasclerotic pre-procedural ABI (≥ 1.3). Table 17 summarizes the respective hazard ratios, confidence intervals and p -values.

Compared to an ulcer, gangrene was significantly more strongly associated with amputation during the whole follow-up period ($p=0.014$, $HR=2.6$; 95% CI 1.2–5.4).

The independent risk factors associated with the overall need for secondary bypass surgery were an urgent procedure ($p=0.024$, $HR=2.7$; 95% CI 1.1–6.6) and a vessel-related complication during the primary procedure ($p=0.044$, $HR=3.1$; 95% CI 1.03–9.6).

The significant predictors of any re-intervention were gangrene ($p=0.000$, $HR=2.6$; 95% CI 1.6–4.5), a vessel-related complication during the primary procedure ($p=0.004$, $HR=3.7$; 95% CI 1.5–9.0) and former arterial thrombosis ($p=0.000$, $HR=3.5$; 95% CI 1.9–6.5).

The independent risk factors for the need for endovascular re-interventions were a mediasclerotic pre-procedural ABI (≥ 1.3 ; $p=0.003$, $HR=4.0$; 95% CI 1.6–10.3) and gangrene ($p=0.032$, $HR=2.4$; 95% CI 1.1–5.2).

Study IV

In the first round of evaluation, the κ_{free} between all observers was 0.32 with a range of 0.11–0.54 between two observers, a mean of 0.27 and a median of 0.15.

After the intervention, the inter-observer agreement increased, but still remained below the adequate inter-observer agreement: κ_{free} between all observers was 0.49 with a

TABLE 17
Independent risk factors associated with the overall amputation rate

	HR (95% CI)	<i>p</i> -value
Urgent procedure	2.7 (1.3–5.6)	0.007
Inability to ambulate	3.8 (1.9–7.7)	0.000
Gangrene	2.5 (1.2–5.2)	0.012
ABI ≥ 1.3	2.2 (1.1–4.5)	0.023

HR=hazard ratio, CI=confidence interval

range of 0.2–0.56 between two observers, a mean of 0.37 and a median of 0.36.

Agreement between two observers varied from 38% to 69% in the first round and between 51% and 73% in the second round. Agreement between all seven investigators was reached in only 7% and 19% of the cases in the first and second round, respectively. Even among the three most experienced observers, the κ_{free} was only 0.49 at its highest in the second round.

Because there are several lesion types that do not fit any of the TASC II classes, an attempt was made to increase inter-observer agreement by combining classes. Only when classes A and B were combined, with classes C and D remaining separate, was there adequate inter-observer agreement as the κ_{free} reached a value of 0.71 in the second round.

Study V

The clinical symptoms were described in 346 (99%) of the referrals, ABI values were reported in 166 (47%) and toe pressures in 193 (55%) of the referrals. Pulse palpation status was included in 103 (29%) referrals. All key pieces of information were included in 69 (20%) referrals, whereas in 112 (32%) referrals the informational content was unsatisfying, as 107 (31%) of these included only one key piece of information and five (1%) included no relevant information about the patient. When procedures were performed on the basis of the referrals including all the key pieces of information, the complication and/or technical failure rate was 7 (10%), while this figure was 22 (20%) for those with unsatisfying informational content ($p=0.009$).

A total of 151 (43%) referrals led to DSA only, 173 (49%) referrals to PTA and 27 (8%) to stenting.

Problems in crossing the arterial lesions with a guidewire and technical difficulties due to, for example, kinking of the catheters

led to 30 (9%) procedures being complete immediate technical failures. In 16 (5%) cases, PTA was successful in only a part of the arterial lesions, as attempts to treat lesions at multiple levels were not all successful. A complication (vessel perforation, distal embolization or thrombosis) occurred in 13 (4%) procedures.

A vascular surgeon was consulted on 14 (4%) of the occasions, and a vascular surgeon was a co-operator on 24 (7%) occasions.

In 270 (77%) of the cases, the imaging or the procedure performed at the Department of Radiology corresponded to the request made in the referral letter, or a vascular surgeon was a co-operator or consulted before changing the strategy.

Altogether, the radiologist independently performed endovascular interventions that were not requested on 74 (21%) occasions.

In 7 instances where a specific intervention was requested based on other vascular imaging, the intervention requested in the referral was performed successfully, but additional lesions were also treated at the independent decision of the radiologist. Of these cases, problems were encountered in 86%, as 1 led to a complication and 5 were immediate technical failures.

On 70 (20%) occasions, an endovascular procedure was performed even if only DSA was requested. In only 2 of these, a vascular surgeon was consulted before extending the DSA to an intervention, and in 1 of them a vascular surgeon was a co-operator.

When the interventional radiologist independently made the decision to perform an intervention not requested in the referral, the result was a complication and/or a technical failure significantly more often ($p=0.007$) than when the referral request was followed or a vascular surgeon was consulted beforehand.

In 7 (2%) instances, less was done than what was requested due to, for example, patient-related problems (e.g., restlessness). ☹

Discussion

Outcomes of infrainguinal revascularization for CLI

At present, the BASIL trial remains the only one large multicentre randomized controlled trial comparing bypass surgery and endovascular interventions for SLI (ADAM ET AL. 2005). The inclusion criterion was based on uncertainty – that is, the vascular surgeon and the interventional radiologist believed it was appropriate to offer the patient either revascularization method. As a result, only 10% of all SLI patients presenting at the centres involved in the study were actually enrolled, demonstrating low external validity (CONTE 2010A). This problem has also been encountered in other randomized trials; the higher the requirement for internal validity, the fewer patients are eligible for the study (CULL ET AL. 2010, LEPÄNTALO ET AL. 2009). On the other hand, the strength of a registry-based study is the large coverage of the patients in daily practice and the avoidance of selection bias. However, in non-randomised observational studies, investigators have no control

over treatment assignment and the patient groups tend to differ in terms of risk factors and arterial lesions treated. This problem can be partially compensated for by using balancing scores such as the propensity score. It is a multivariable statistical method that identifies patients with similar chances of receiving one or the other treatment, thus permitting non-randomized comparisons of treatment outcomes (BLACKSTONE, 2002). In Studies I and II, the propensity score was used for regression adjustment and for one-to-one matching. In both studies, the one-to-one propensity score matching resulted in treatment groups with very similar measured covariates. The area under the ROC curve for the obtained propensity score was satisfactory, especially considering the fact that the differences between the study groups – i.e., patients undergoing two different treatment methods – are likely to be less marked than what is often

observed among patients with or without an outcome endpoint.

AFS is considered the most important outcome endpoint in the treatment of CLI (NORGREN ET AL. 2010). In Study I, arterial lesions in the femoropopliteal segment were treated, and there was no significant difference in AFS between the two treatment groups after risk adjustment. However, bypass surgery was associated with significantly better leg salvage in the long term when compared to PTA. This might imply possible benefits of treating CLI patients with probable longevity with bypass surgery as the first-line strategy.

On the other hand, in Study II, procedures extending to infrapopliteal arteries were performed with or without simultaneous treatment of femoropopliteal lesions, and there was no significant difference between the two revascularization methods in terms of AFS or limb salvage. In fact, in the subgroup analysis on patients who underwent isolated infrapopliteal revascularization, leg salvage was actually significantly better in the PTA group. Nevertheless, in this subgroup analysis, the freedom from surgical re-interventions was significantly lower in the PTA group, implying that active redo-surgery policy is mandatory to achieve appropriate outcome.

In the BASIL trial, the need for re-interventions was higher in the PTA-first group when compared to the surgery-first group. Also in Studies I and II, the freedom from surgical re-interventions was lower in the PTA group across the board. This is in concordance with previous reports of inferior patency of the endovascular approach compared to surgery (ROMITI ET AL. 2008). It is also due to our general practice: if CLI symptoms are not relieved and the endovascularly treated segment has occluded, the threshold for surgical re-intervention is relatively low. Redo-PTA is opted for only in cas-

es with mild to moderate recurrent symptoms.

The freedom any re-intervention was similar between the two revascularization methods in Studies I and II. Most probably our active surveillance policy on venous grafts and the mostly endovascular treatment of graft stenoses were the reasons for the equal rates of any re-interventions between the treatment groups.

Nonambulatory status upon hospital arrival was independently associated with all the primary outcome measures as well as with overall mortality and amputation in Study III. Here, chronically bedridden patients were not revascularized. The ambulatory status was recorded upon hospital arrival and hence the mobility of the patient could have been better before the onset of CLI. In the elderly, the general condition often deteriorates quickly when patients lose their ability to walk. The nonambulatory patients also often have more comorbidities than those ambulating independently, and the loss of mobility may also be a sign of the patient's worsening overall condition and not necessarily a reflection of local ischaemic leg symptoms. Moreover, as the nonambulatory status was an independent predictor of secondary bypass surgery at 6 months, it might be that secondary surgery brought upon adverse events or increased physical burden thus further contributes to the poor prognosis observed here. The results of the study further support those of previous investigations in which the CLI patient's impaired preoperative mobility has been associated with poor outcome even in the presence of a patent graft (FLU ET AL. 2010, SIMONS ET AL. 2010, TAYLOR ET AL. 2009).

In Study III, gangrene was an independent risk factor for amputation and was significantly more strongly associated with it compared to ulcer. As a matter of fact, ulcer did not differ from rest pain as a risk factor for amputation in the present series. Simi-

lar results have been demonstrated in earlier studies (BIANCARI ET AL. 2007, TAYLOR ET AL. 2009). Gangrene is always a consequence of markedly reduced circulation, while an ulcer may also have other aetiological components, such as neuropathy. Consequently, the healing of an ulcer may be more likely when offloading is achieved together with revascularization than when gangrene is present. Nevertheless, the most commonly used clinical classifications for CLI include ischaemic ulcer and focal gangrene in the same class, and they are often discussed as one entity, namely tissue loss (FONTAINE ET AL. 1955, RUTHERFORD ET AL. 1997).

If a patient presented with the two independent predictors discussed above, non-ambulatory status and gangrene, the outcome was extremely poor – after 6 months, 67% had died or lost their limb and after one year this figure was 83%.

Significance of the TASC II classification for femoropopliteal arterial lesions

The TASC II document provides the currently most widespread and applied classification of the morphological changes in the lower limb vasculature in PAD (NORGREN ET AL. 2007). The four different grades in this classification are based on several elements, such as the type of lesion (stenosis or occlusion) as well as the number, length and localisation of the lesion. This illustrates that, occasionally, disagreement arises, when the classification is applied in clinical practise. On the other hand, the classification of arterial lesions can be rather difficult, as most cases of PAD, especially CLI, requiring intervention are characterized by more than one lesion at more than one level.

The poor inter-rater agreement in the first round of the study came perhaps as no surprise, as the observers classified the lesions on the basis of self-education using the printed TASC II document. Nonetheless,

even after two educational interventions, the inter-observer agreement remained poor. Since the publication of the present study, the poor reproducibility of TASC II classification has also been demonstrated in other studies (BRADBURY ET AL. 2010C).

There are some shortcomings related to the TASC II classification of femoropopliteal lesions. Firstly, no definition for stenosis or total occlusion is provided. Because the lesions may be complex and consist of segments with milder and more severe stenoses and occlusions, variations occur in the interpretation of lesion length and number. Furthermore, the delineation of heavily calcified lesions by viewing angiograms is a potential source of inter-observer variability, and the degree of calcification cannot even be reliably estimated on MRA, which is currently the preferred preoperative imaging modality in many centres (LAKSHMINARAYAN ET AL. 2009, NORGREN ET AL. 2007). Moreover, some of the written definitions of the lesions do not match the illustrations, creating confusion. Lastly, some lesion patterns do not fit any of the TASC II classes, which contributes to the decline in inter-observer agreement. A more complex classification would be required to adequately describe the femoropopliteal arterial lesions, but then again, this might lead to decreased applicability of the classification in daily practice.

Communication and decision-making during angiography

The communication between the vascular surgeon and interventional radiologist is frequently based only on the referral text. Therefore, it is mandatory that it contain adequate data to allow the optimal treatment of CLI patients. This study revealed that the information value of the referrals made by vascular surgeons was rather poor, as the majority of them were incomplete. The proportion of complications and/or technical failures of the endovascular interventions performed according to a poor refer-

ral was twice as high as of those executed on the basis of a good referral. Although this difference did not reach statistical significance, it points to the importance of the referral's good informational quality. Therefore, more effort is required from the vascular surgeons to improve the informational content of their referrals to facilitate the evaluation of the proper approach and planning of DSA with or without intervention.

In the majority of the cases, the execution of imaging or interventions at the Department of Radiology corresponded well with the referral. On the other hand, the radiologists made treatment decisions of their own in 21% of the instances. This seemed perhaps unnecessarily risky, as these interventions resulted in significantly more complications and/or technical failures than those executed on request. After all, in the BASIL trial, patients who underwent surgical bypass after an initial failed angioplasty did fare significantly worse than those who were initially treated with bypass surgery (BRADBURY ET AL. 2010D). Moreover, the overall clinical responsibility for a CLI patient's treatment strategy is also legally designated for the vascular surgeon.

A mixed team approach could help to decrease problems in communication. Efforts to improve the communication and multidisciplinary teamwork have been made, as each day one of the vascular surgeons is assigned to be the vascular consult and since 2007 two vascular surgeons have regularly performed endovascular procedures at the department of radiology. At our clinic, the radiologists do not participate in the clinical evaluation of CLI patients. This could, however, make the teamwork stronger and justify therapeutic decision-making also for the radiologist.

Study limitations

A concern for data validity and completeness is typically associated with registry-

based studies, which is the nature of Studies I–III. Efforts were made to minimize these limitations. Our vascular registry includes all patients that have undergone any type of revascularization, endovascular or surgical. The completeness of the registry data has been checked against hospital registries, and missing data have been completed afterwards. The key outcome endpoints were double-checked against official national registries. Yet, no registry is immune for omissions and differences in the interpretation of the data (KANTONEN ET AL. 1997, TAHA ET AL. 2008).

In Studies I and II, the one-to-one propensity score matching resulted in treatment groups with very similar measured covariates, yet we were unable to include the characteristics of treated lesions as an unambiguous covariate. The anatomy of the treated lesions was registered according to the TASC II classification. However, this was not included in the analysis due to the poor inter-rater agreement in grading the femoropopliteal arterial lesions that was observed in a previous study of ours (Study IV). As the patients who undergo bypass surgery tend to have a more widespread configuration of arterial occlusive disease, the lesions treated by PTA were probably shorter and less severe than those treated surgically.

The difference in the routine surveillance protocol of the two revascularization strategies is additionally a possible limitation of Studies I and II. Even though all patients were followed until their symptoms subsided and/or wounds healed, routine clinical examination and ABI measurements were performed up to 4 weeks post-procedurally for the PTA group, whereas they were performed up to 12 months alongside DD for the bypass surgery group. It is therefore probable that the first signs of re-stenosis and limb ischaemia were detected earlier in the bypass surgery group. Even though there is no consensus to date on how endovascularly treated patients should best be

followed, our surveillance protocols have recently been changed so that they are now identical for both, the surgical and endovascular, revascularization strategies.

The dual antiplatelet therapy with clopidogrel and aspirin for one month after an endovascular procedure has been in routine use at our clinic since 2001. However, there is variation in the postinterventional antithrombotic medication policy from centre to centre. There is no direct evidence to support the use of dual antiplatelet therapy after infrainguinal PTA, and this regimen has principally been adopted on the basis of data from the coronary field (CHEN ET AL. 2005, MEHTA ET AL. 2001, YUSUF ET AL. 2001). Moreover, the proportion of stents currently used infrainguinally in the treatment of CLI is increasing and is significantly higher in many centres compared ours (CONRAD ET AL. 2011). Therefore, the results of Studies I–III might not be directly transferable to everyday clinical practise in many centres. In our centre, a selective stenting policy has been adopted, since the current data does not support routine stenting over selective stenting (KASAPIS ET AL. 2009, TWINE ET AL. 2009). For instance, in the meta-analysis by Kasapis et al. including 10 RCTs with a total of 1,343 patients and 1,442 limbs, no definitive evidence favouring one stenting strategy over the other was found. Given the absence of data to the contrary and the lower equipment cost, the authors conclude that selective stenting should remain the preferred endovascular therapy.

Furthermore, possible limitations of Study III are the relatively small numbers of patients, especially in the subgroups, and a relatively short follow-up. Additionally, the retrospective nature of the study and the absence of a control group may cause bias.

In Study IV, the length of the lesions was not accurately measured with an electronic measure during the classification process,

which can be considered a weakness of the study and a possible explanation for poor inter-observer agreement. Additionally, increasing the time spent grading each case might have improved the agreement. However, the outcome was no better among a subgroup of very experienced investigators who were highly familiar with this particular classification system.

The weakness of Study V is its retrospective nature. 🐼

Conclusions

1. When technically feasible, infrainguinal PTA seems to be a valid alternative for bypass surgery in the treatment of CLI when redo-surgery is actively utilized. However, in the treatment of femoropopliteal lesions, PTA might be associated with poorer leg salvage in the long term when compared to bypass surgery, although treatment method did not affect AFS. Bypass surgery could likely be considered as a better alternative in patients with probable longevity.
2. Strong predictors of poor outcome after PTA for patients with CLI are cardiac morbidity, nonambulatory status upon hospital arrival and gangrene as a manifestation of CLI. Gangrene is significantly more strongly associated with the risk of limb loss than ulcer.
3. The TASC II classification of femoropopliteal arterial lesions allows individual interpretations, and its reproducibility seems to be rather poor. Its common use as a basis for therapeutic decision-making and for reporting outcomes in scientific literature can therefore be questioned.
4. The communication between vascular surgeons and interventional radiologists seems to be insufficient to ensure optimal treatment for CLI patients. A mixed-team approach could help decrease these problems. 🐼

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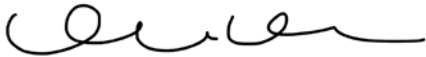
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Helsinki, August 15th, 2011

A handwritten signature in black ink, consisting of a series of loops and a long horizontal stroke at the end.

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Original publications

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The effectiveness of infrainguinal
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